Mineral Fiber Exposure Assessments: What should we measure? What can we measure? Analytical Options

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Conceptual Model

for development of methods for prospective assessment of health risks associated with exposures to mineral fibers

epidemiology

Effects

dose-response

rel. potencies

Dose in tissues

respiration

retention/clearance

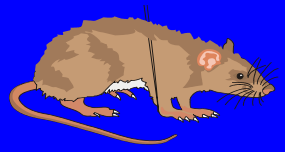
translocation

Exposures

fate/transport

Sources

toxicology



Key question: what dose in tissues/lung should not be exceeded?

Temporal exposure issues - lifetime, short term, early life stages

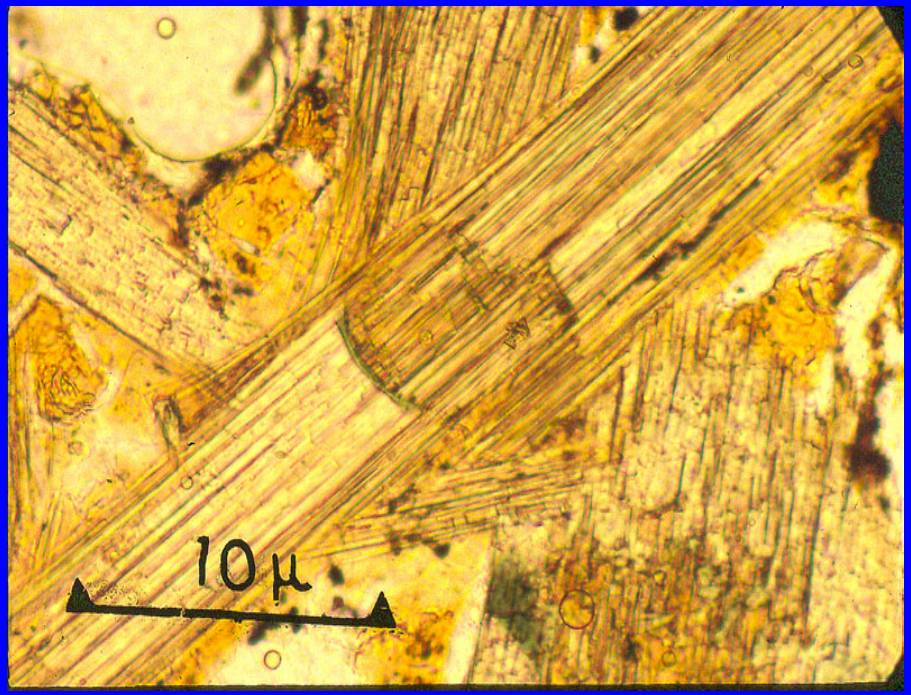
There are many different fiber risk assessment problems. It is therefore logical that requirements for analytical methods will vary and that risk assessors need a suite of methods to choose from and/or use in combination.

Uncertainties for what to measure are an impediment for development of optimum analytical methods for assessing risks from exposures to all durable fibers which may be inhaled.

A Major Complication for Risk Assessors: Mineral Fibers Have Diverse Origins and Properties When Removed from Rocks

Chrysotile asbestos cross-fiber vein

Amphibole crystals in taconite (iron ore) - ferroactinolite replacing hornblende



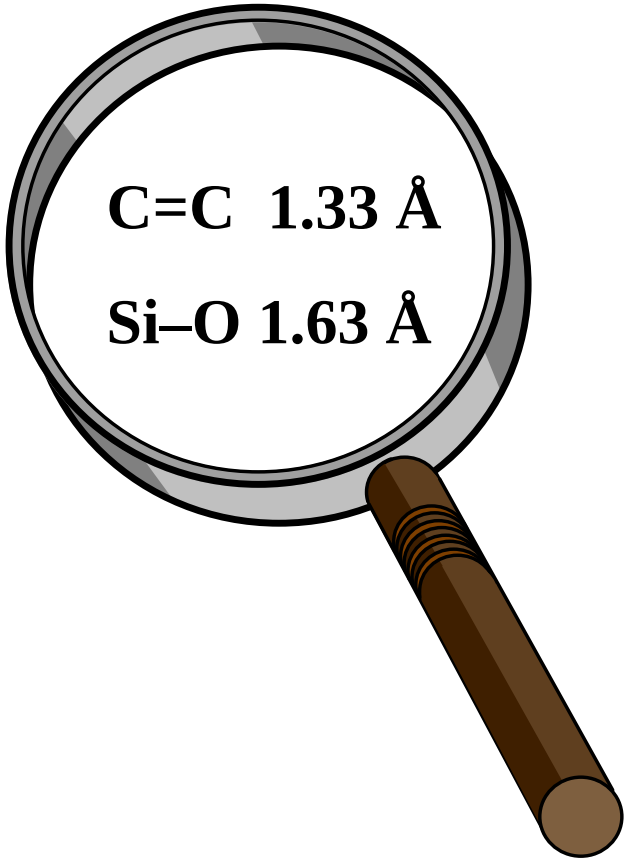
Phagocytosis of asbestos fibers

pulmonary alveolar macrophage cell attempting to engulf and ingest several long crocidolite asbestos fibers

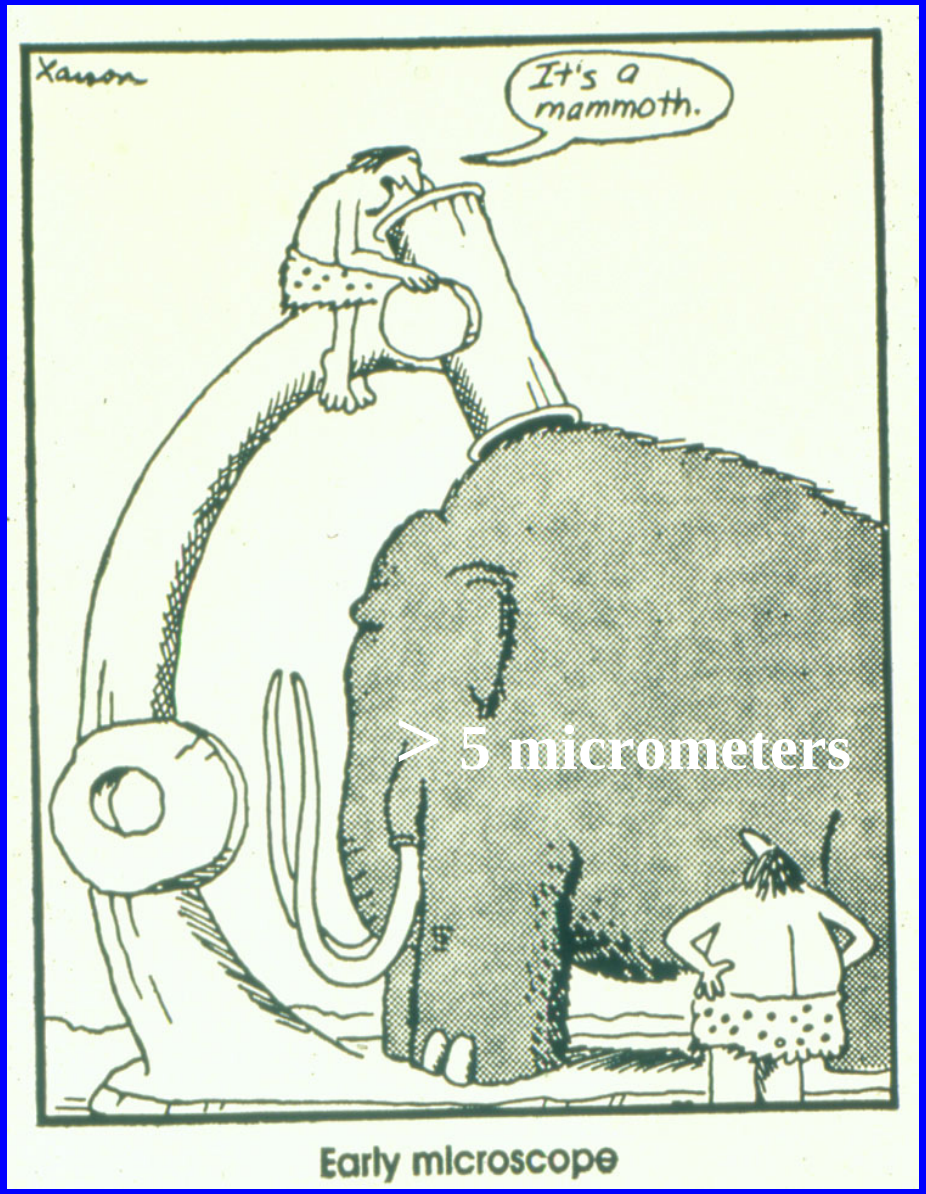
incomplete ingestion of asbestos fibers can lead to extensive ‘selective release’ of proteolytic enzymes and ROS from the ‘frustrated’ PAMs

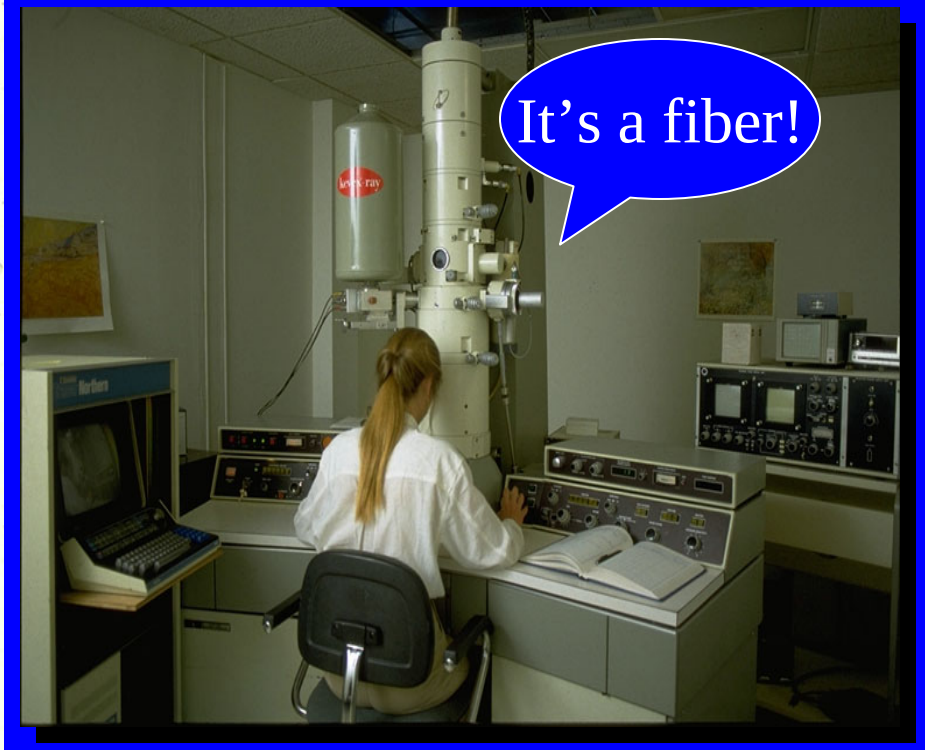
Measures of Small Sizes

- **millimeter (mm) 10^{-3} m**
- **micrometer (λm) 10^{-6} m**
- **nanometer (nm) 10^{-9} m**
- **angstrom (Å) 10^{-10} m**



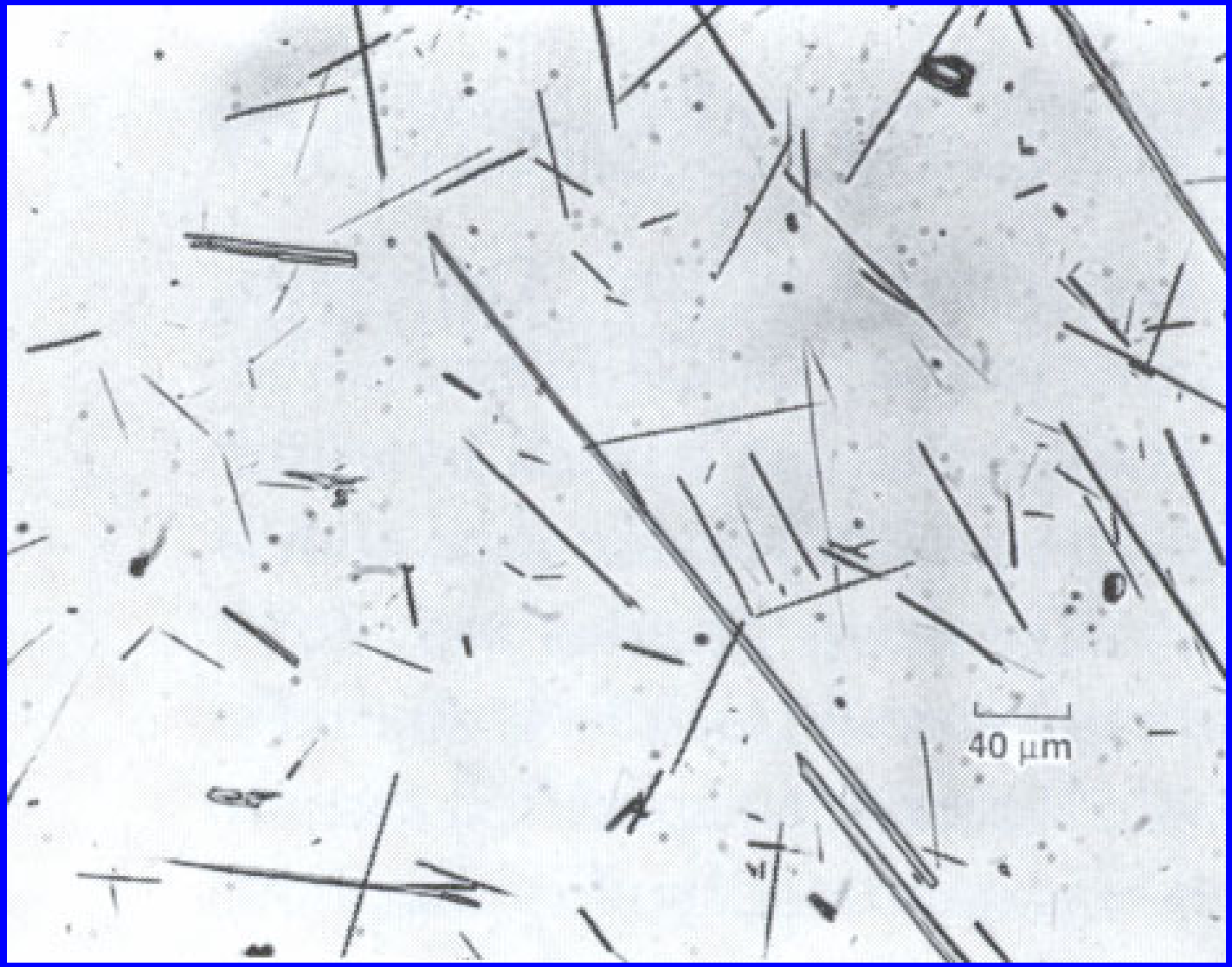
Tempus fugit





Transmission Electron Microscope (TEM)

Tremolite acicular “Cleavage Fragments” ?



Amphibole asbestos fibers have complex crystalline structures that may regulate size and shape changes in response to physical, chemical and biological processes.

Cleavage of asbestiform fibers can occur and the resulting fibers (cleavage fragments?) are unlikely to be less toxic than the original fibers.

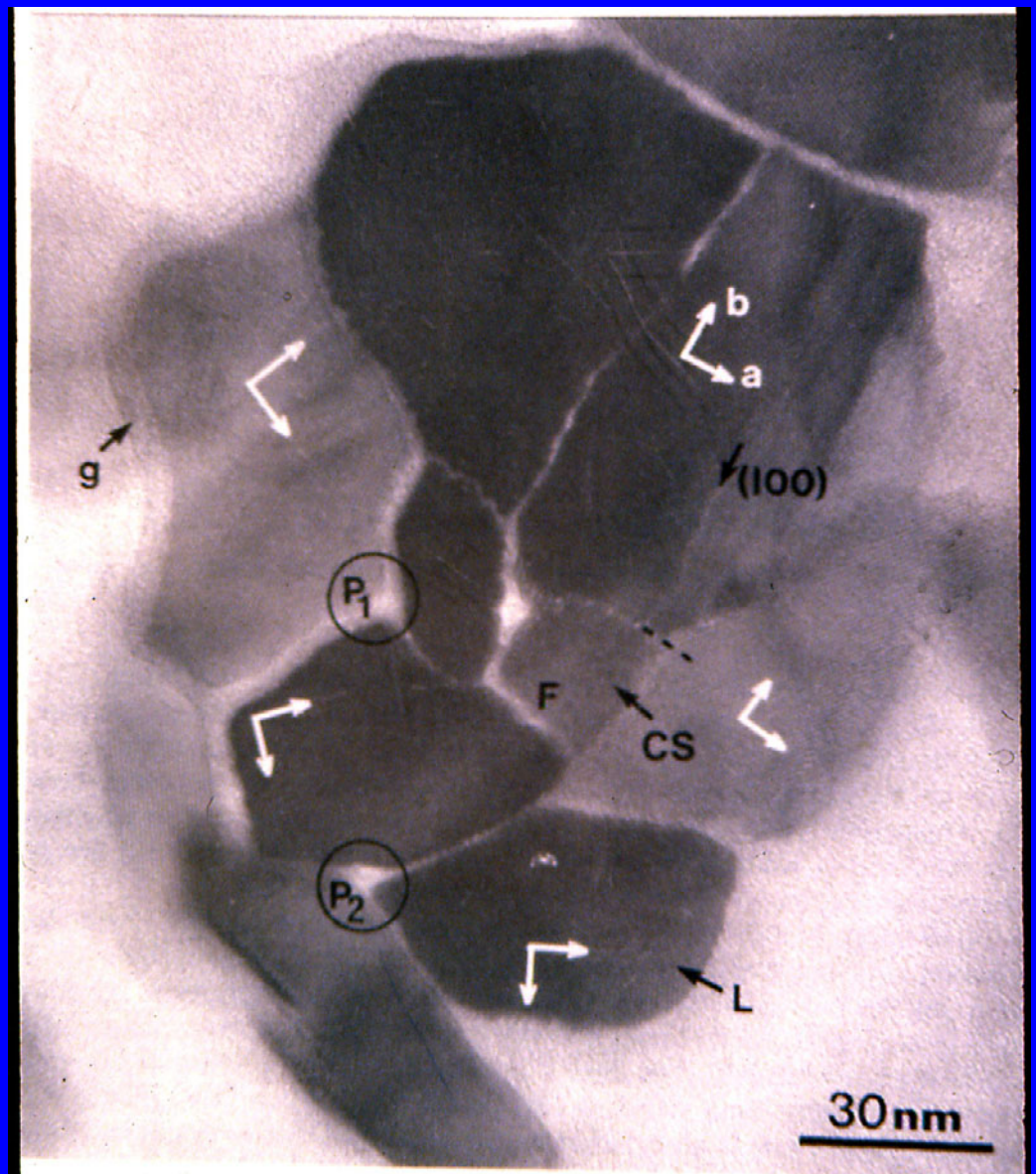


Fig. 2. Lattice image of a transverse section of a crocidolite fibre taken from human blood serum. This image was recorded with *hk*0 beams contributing to the image. See text for details.

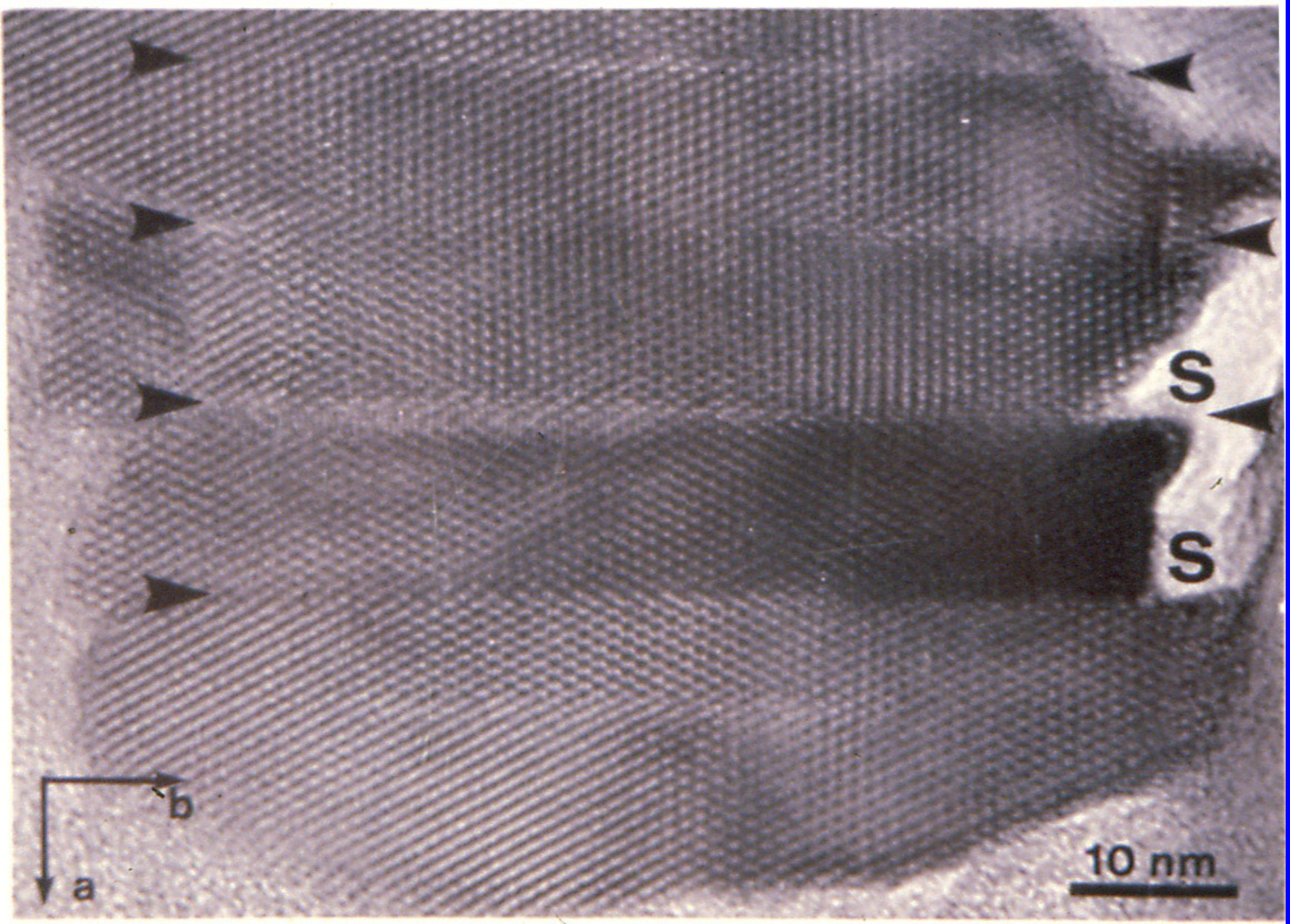
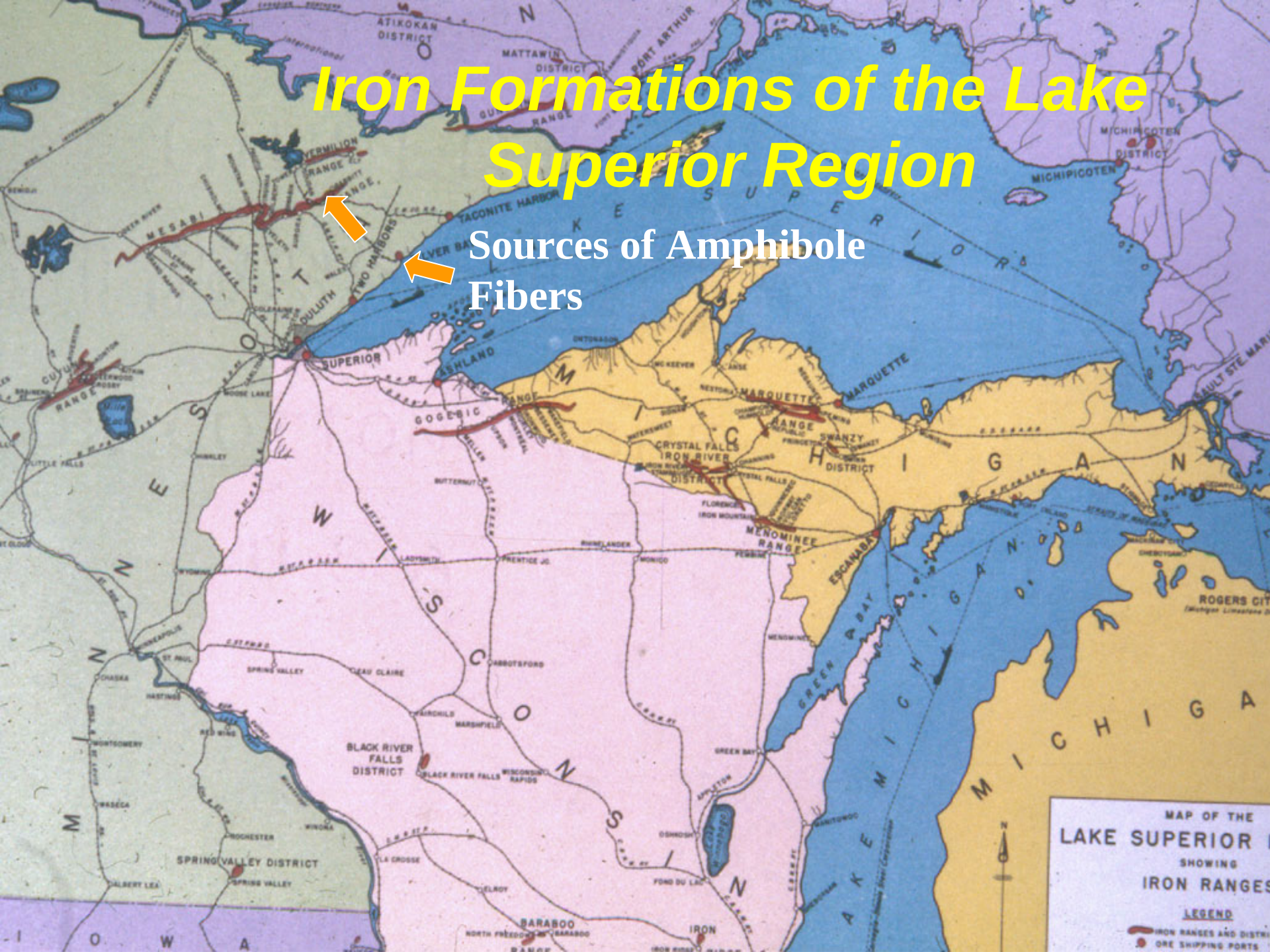


Fig. 3. Lattice image of a transverse section of crocidolite. (100) defects are arrowed. Note the surface steps at S.

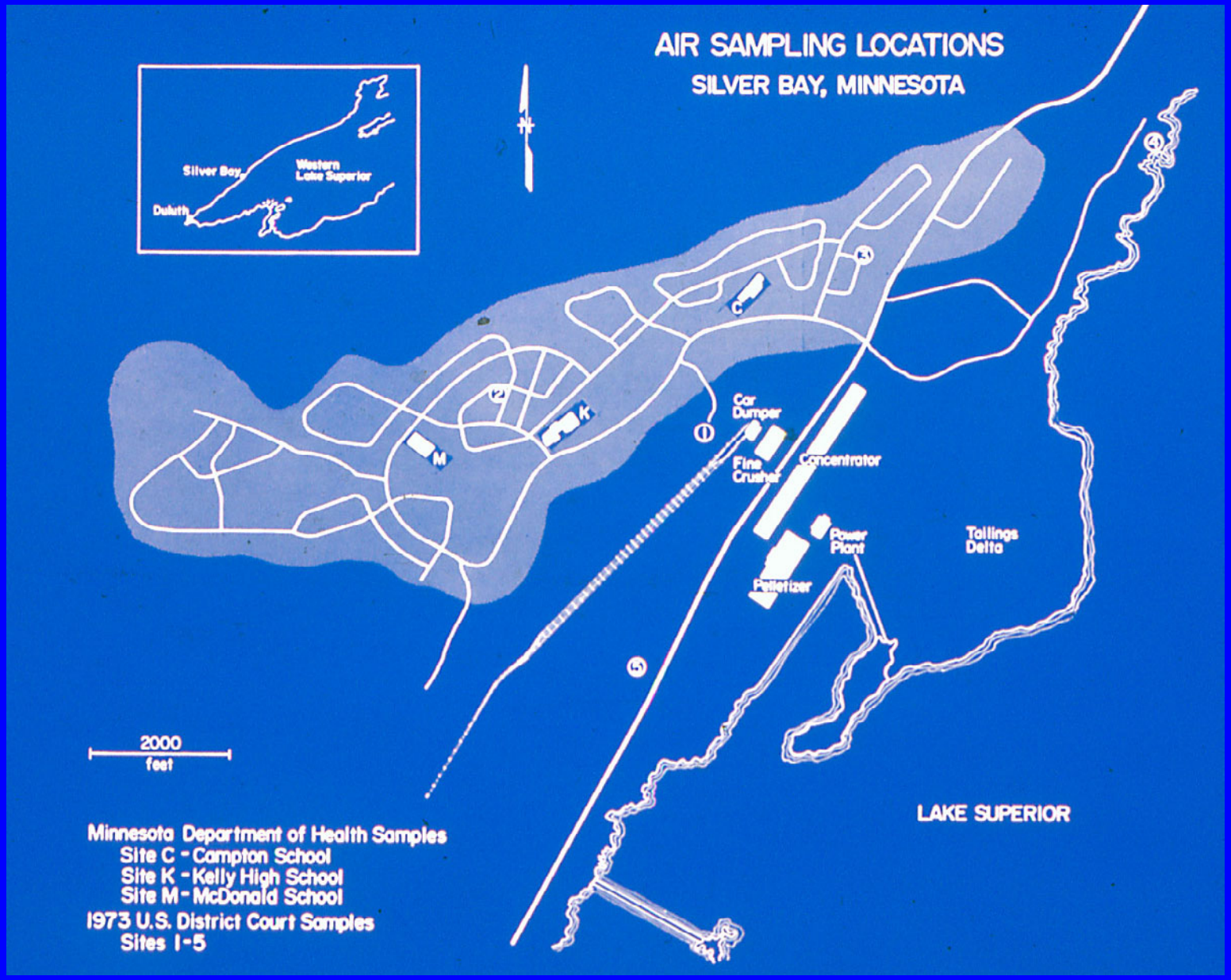
Properties of microscopic fibers that indicate potential for causing asbestos-like pathologies

- Size and shape that allows respiration, retention in lungs, and translocation to pleura
- Durable, persistent in tissues
- Aspect ratio > ? Thinness
- Reactive surfaces, ability to induce ROS
- High collective surface area
- Propensity to split into thin fibers *in vivo*

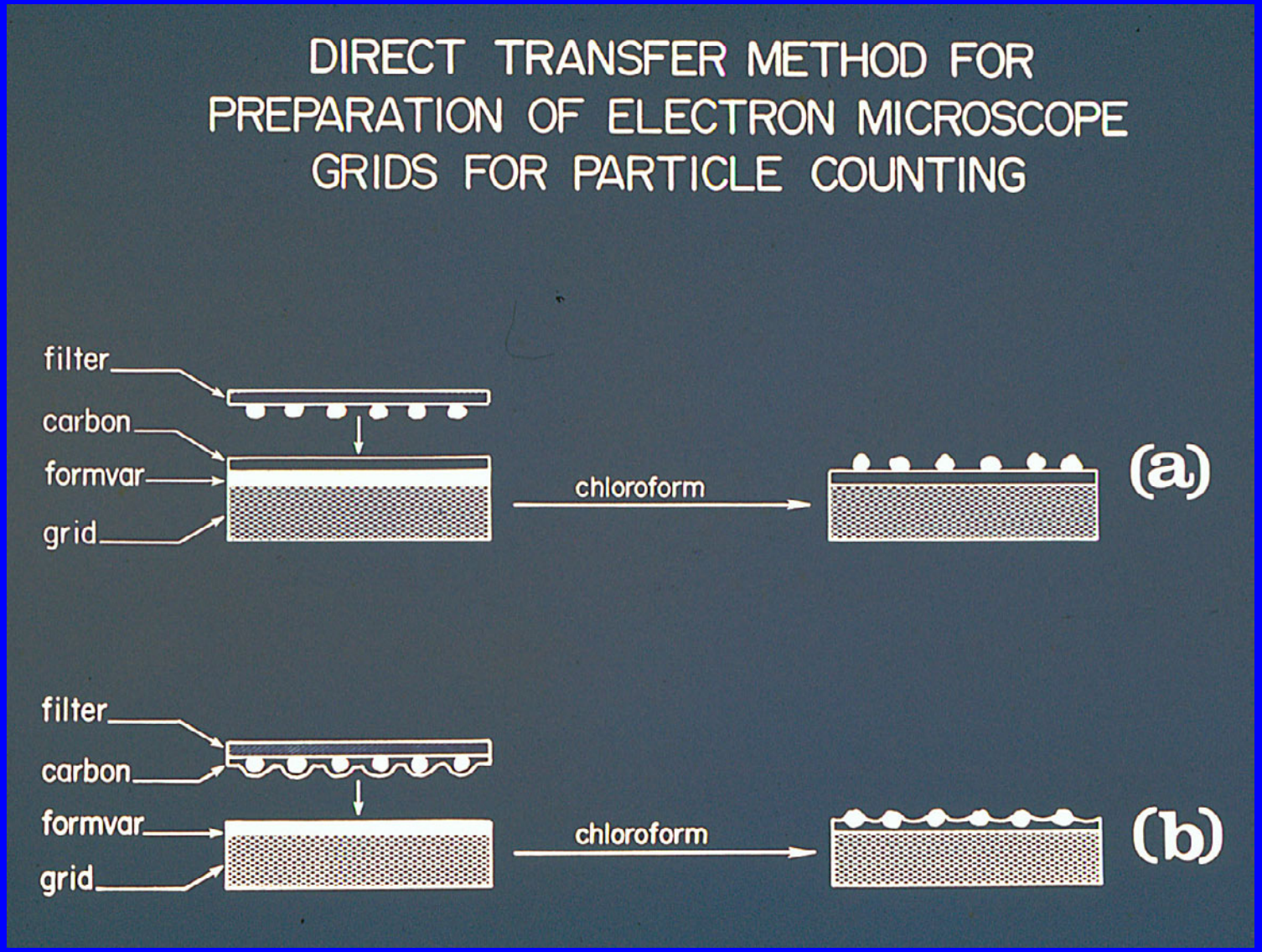
Iron Formations of the Lake Superior Region



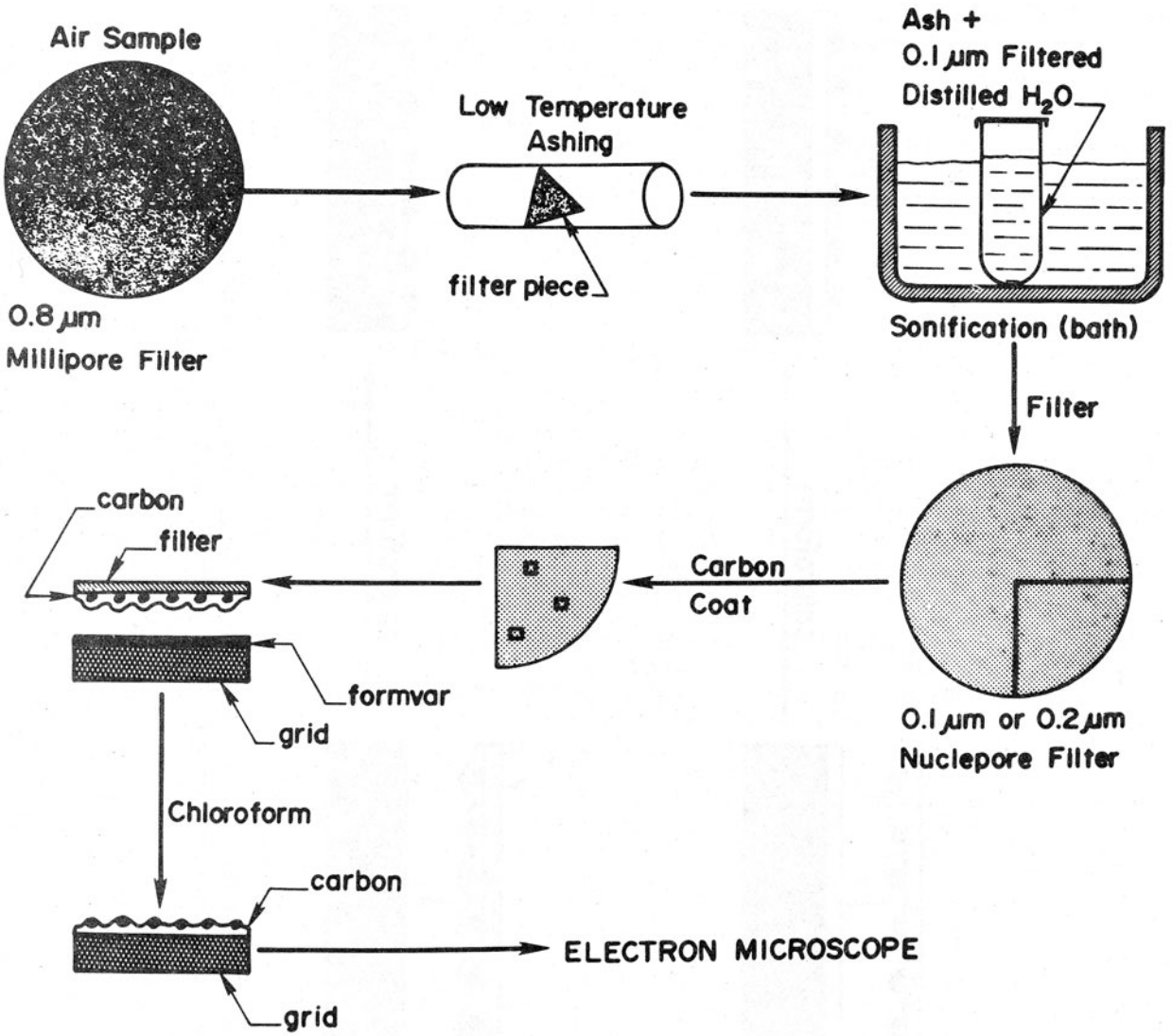
Monitoring Amphibole Fiber Concentrations in Community Air

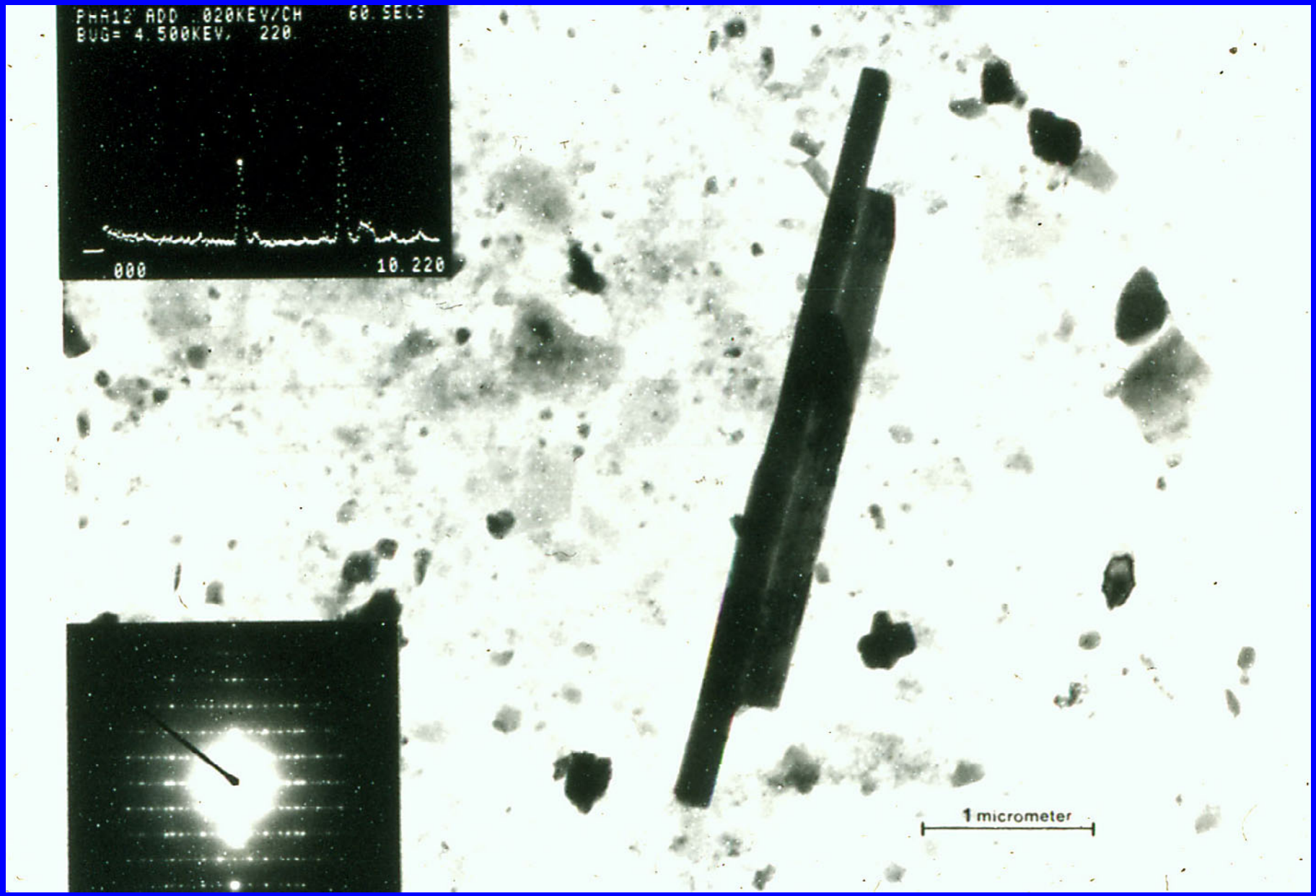


1970s - Fundamental Method for Preparing Grids for Quantitative Particle Analysis with Analytical TEMs

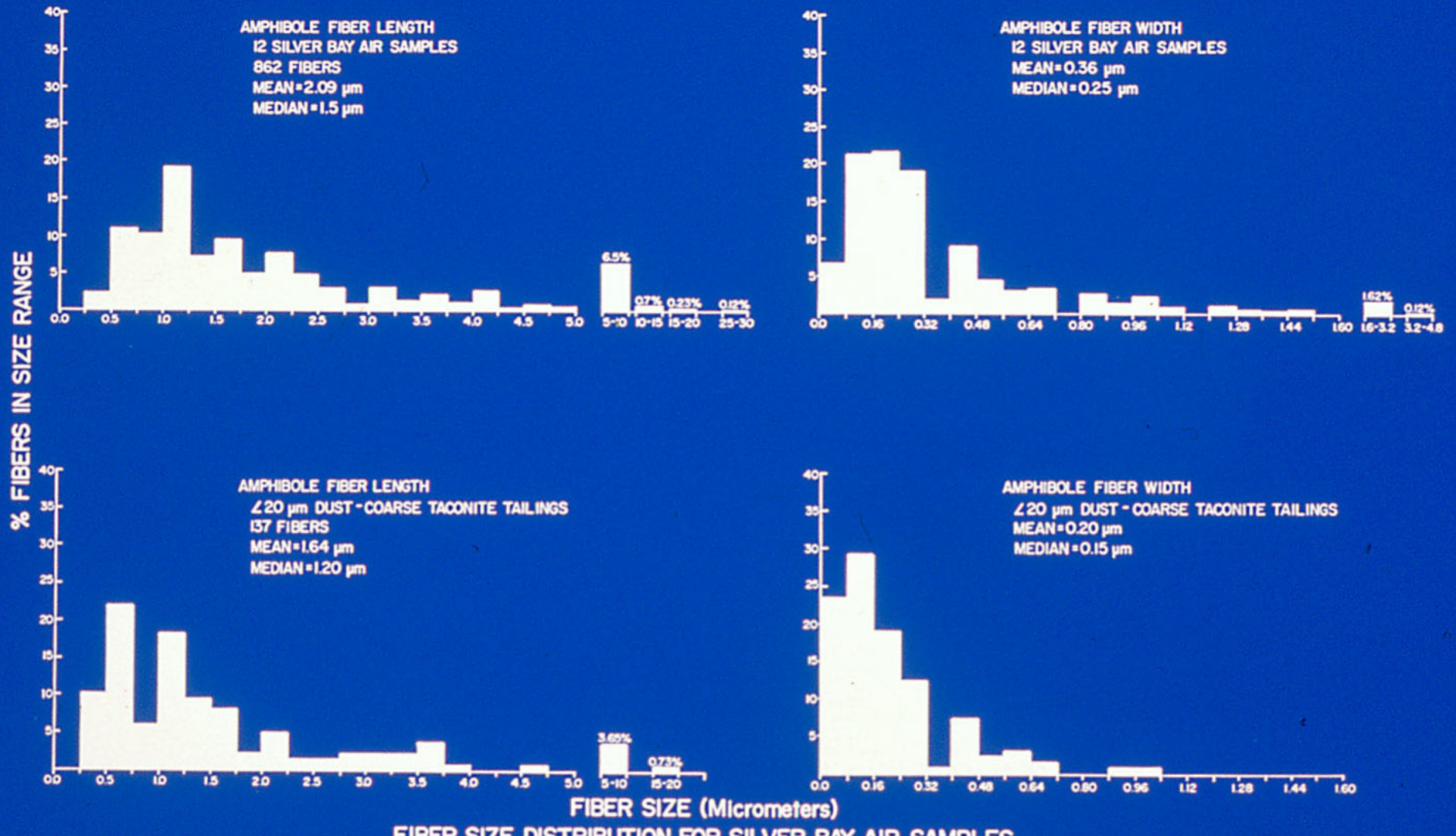


Transfer of Air Samples to Electron Microscope Grids

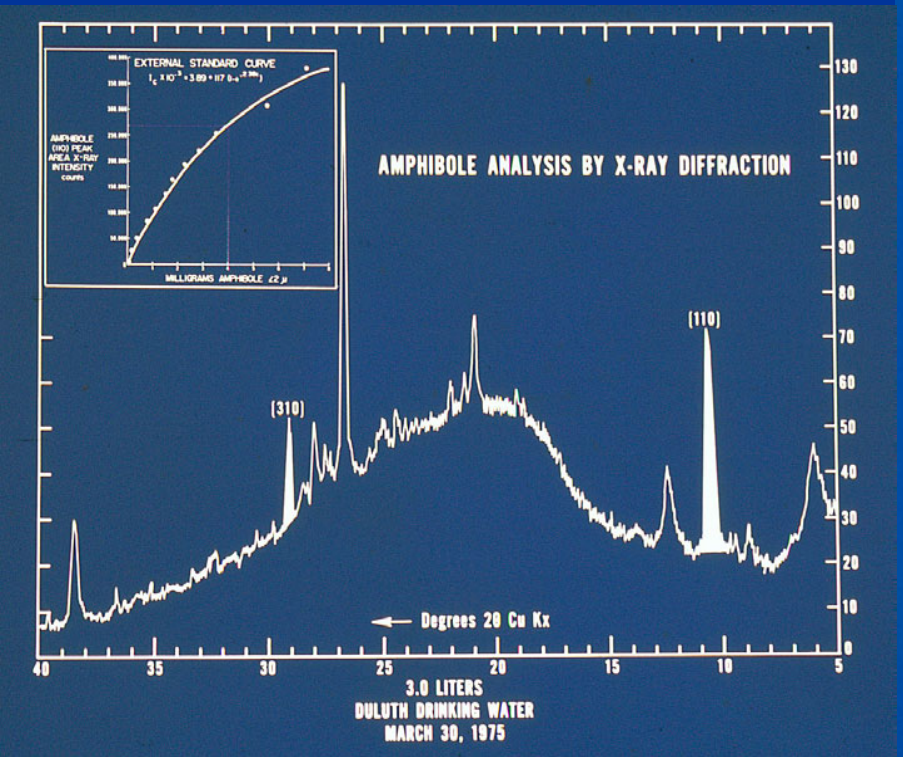


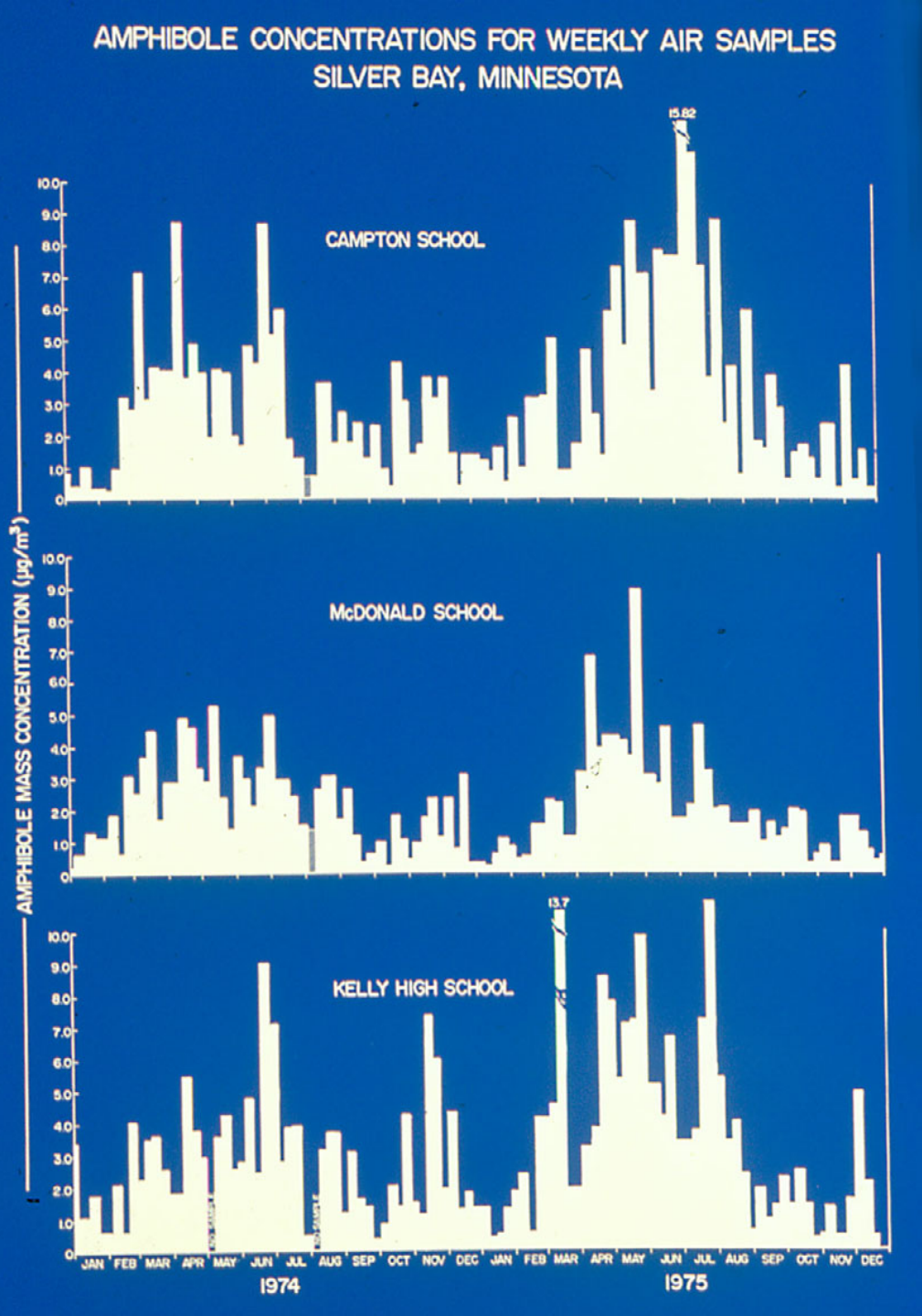

PHA12 ADD .020KEV/CH 60 SECS
BUG= 4.500KEV 220
000
10.220
1 micrometer

Comparison of Amphibole Fiber Size Distributions - Air versus <20 um Tailings



XRD measurement of amphibole mass concentrations in community air from one week high volume air samples: a two year record for three sites





Calibration of XRD Mass Concentration to TEM Fiber Concentration

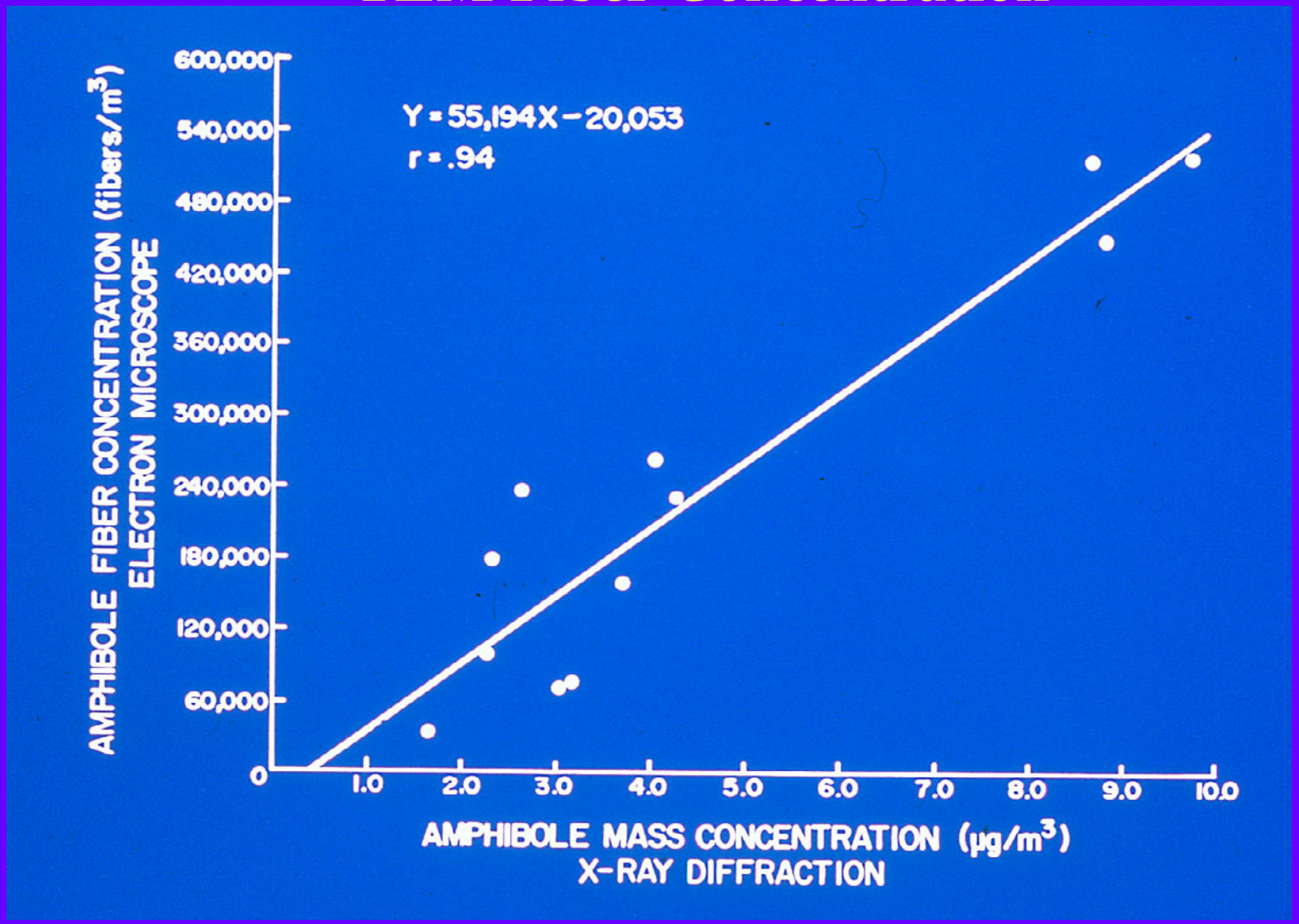


Table 1. MINNESOTA DEPARTMENT OF HEALTH SAMPLES COLLECTED AT SCHOOLS IN SILVER BAY

(amphibole fiber concentrations X 10^{-3})

Sample Number	Amphibole Conc ($\mu g/m^3$) X-ray Diffraction	Amphibole Fibers/Cubic Meter					
		Mt Sinai	EPA/ERL-D	M D Health	Lab A	Lab B	Lab C
7144A	4.08	335	262	390	5.9	5.5	99
7144B	2.64	164	235	177	2.7	5.4	110
7144C	2.34	323	178	174	3.0	6.6	91
9040	8.74	384	513	450	3.9	12.8	100
9041	8.89	502	448	351	2.5	6.1	160
9042	9.82	583	516	569	.8	6.2	291
9061	1.66	53	33	67	1.0	1.6	74
9062	3.05	358	71	112	5.8	12.4	215
9063	3.19	240	76	120	.6	3.8	20
4221	3.73	252	158	138	4.4	10.4	50
4222	2.28	100	99	96	1.4	8.0	70
4223	4.3	394	230	221	3.2	20.6	84
AVERAGE		307	230	239	2.9	8.3	114

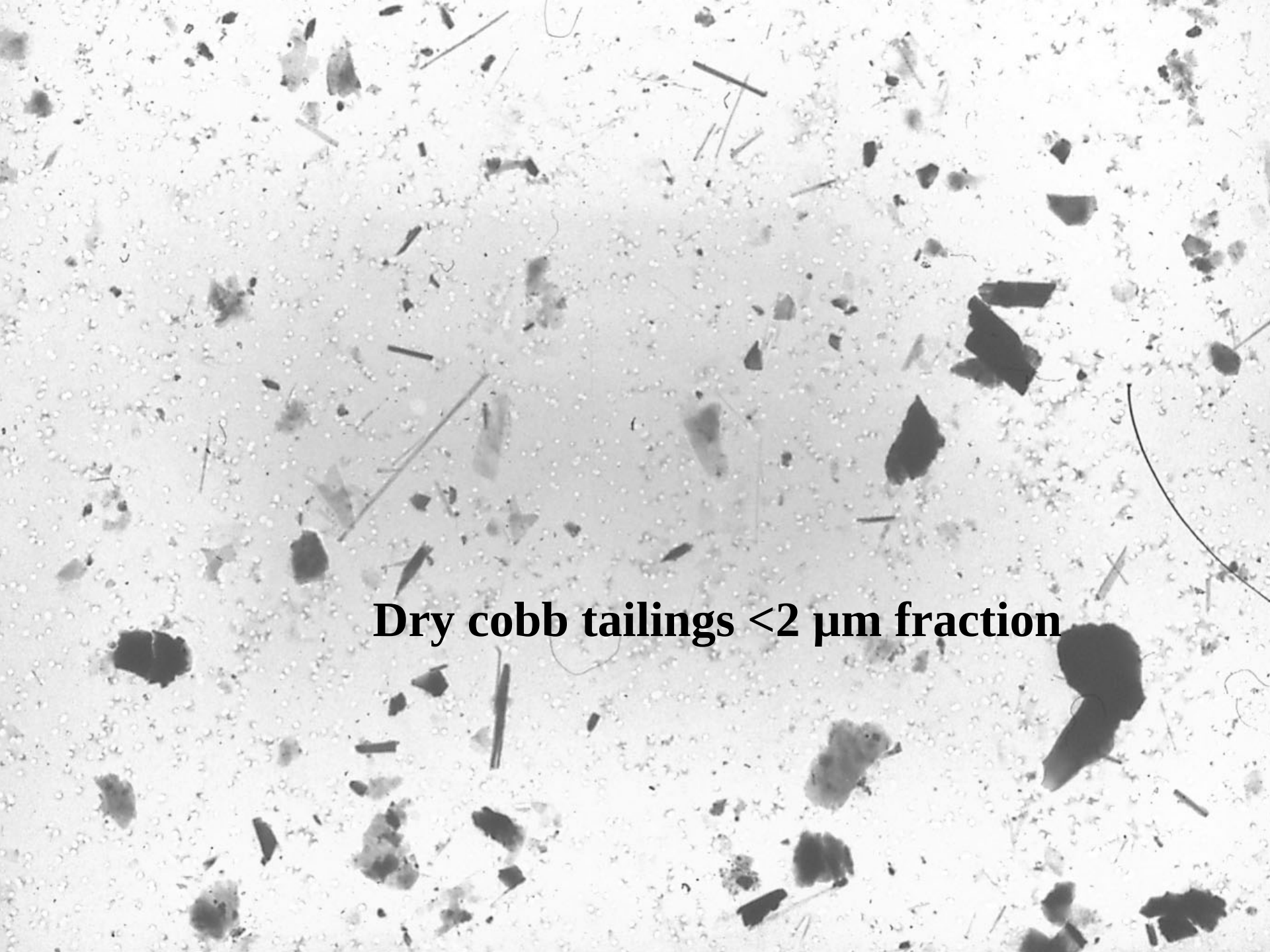
*Samples were collected in December 1974 and March, May and August 1975 at each of three schools.

Table 2. INTERLABORATORY COMPARISON OF MINNESOTA DEPARTMENT OF HEALTH SILVER BAY AIR SAMPLES FIBER ANALYSIS CORRELATION COEFFICIENTS

	X-ray Diffraction	Mt Sinai	EPA/ERL-D	M D Health	Lab A	Lab B	Lab C
X-ray Diffraction	1.00*	0.83*	0.94*	0.89*	0.06	0.15	0.59
Mt Sinai	0.83*	1.00	0.77*	0.82*	0.18	0.33	0.69
EPA/ERL-D	0.94*	0.77*	1.00	0.93*	0.01	0.15	0.52
M D Health	0.89*	0.82*	0.93*	1.00	0.07	0.05	0.59
Lab A	0.06	0.18	0.01	0.07	1.00	0.43	0.06
Lab B	0.15	0.33	0.15	0.05	0.43	1.00	0.04
Lab C	0.59	0.69	0.52	0.59	0.06	0.04	1.00

* = Significant correlation at 99.5% confidence level.

TEM and XRD Methods Can Be Adapted to Many Types of Samples

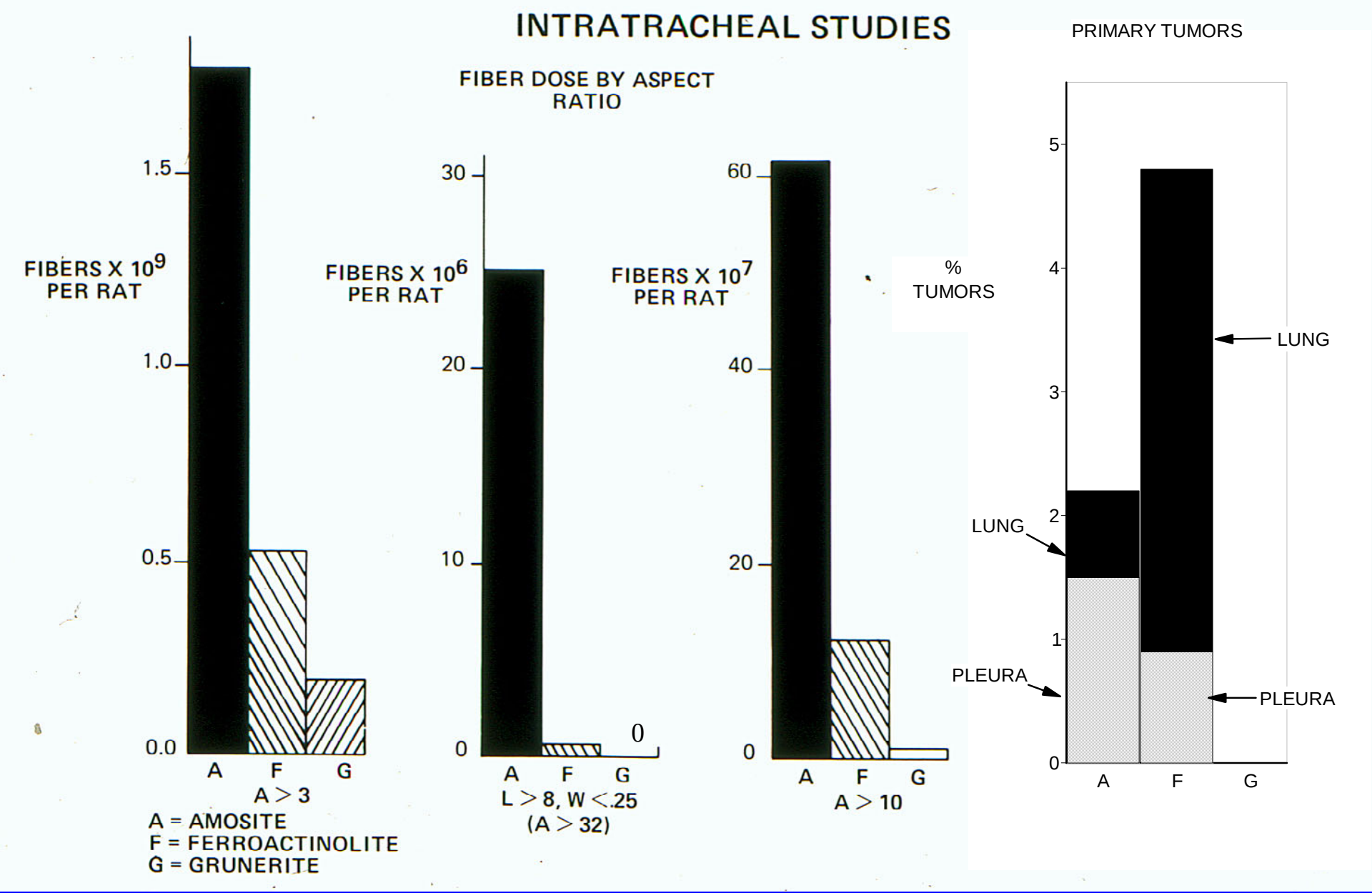

Dry cobb tailings <2 µm fraction

Background

- Concerns for risks associated with non-occupational exposures to mineral fibers (e.g. Reserve Mining Case), and interest in effects of synthetic fibers led to EPA research on effects associated with a wide variety of durable fibers during the period of 1978-1985.
- Determination of carcinogenic potencies relative to known asbestos materials was a major objective.
- The EPA laboratory at Duluth provided electron microscopic characterizations of samples used in biological tests, quantitative measurements of fiber doses in test animals, and determinations of dose-response relationships.
- This research was revisited this year in response to proposals for use of taconite tailings as aggregate.

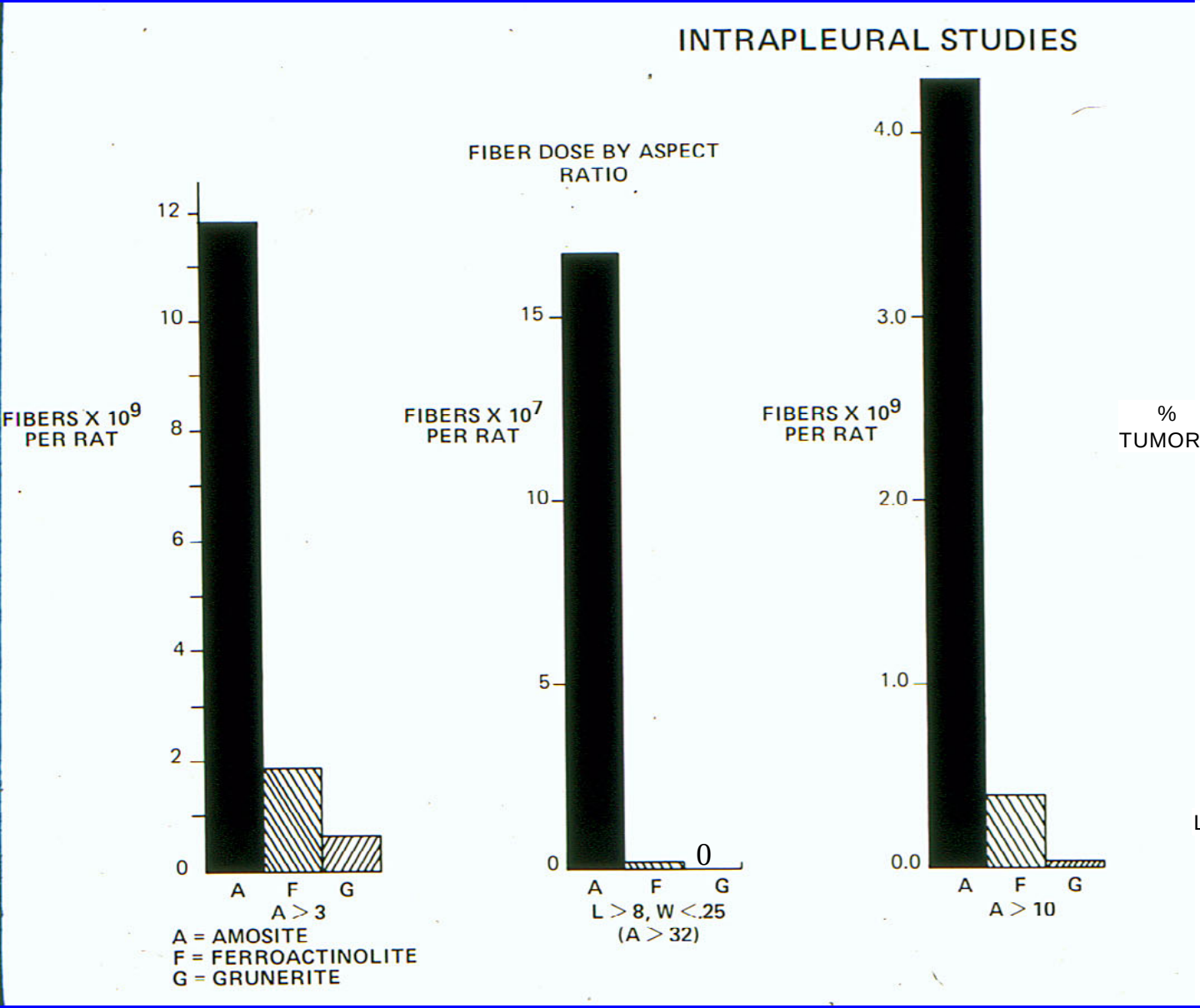
Intratracheal and Intrapleural Exposures of Fischer-344 Rats

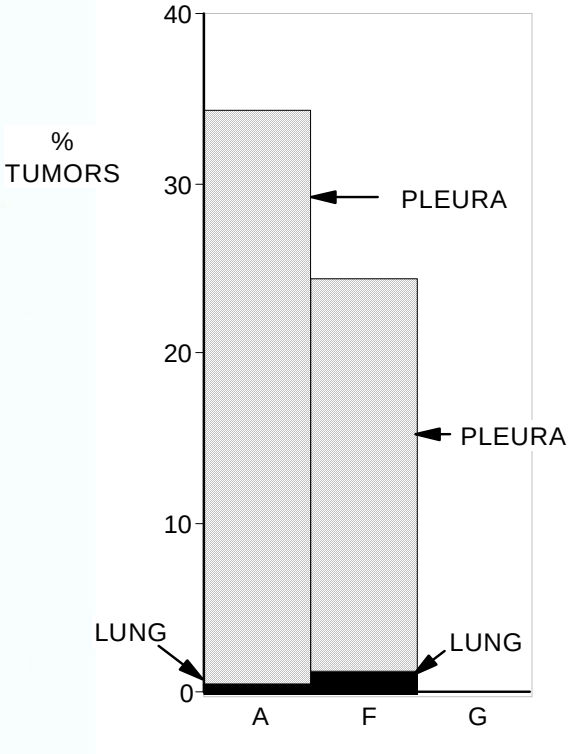
- Primary objective was to determine relative potencies of different fiber types for carcinogenesis
- Studies included two samples of amphibole from taconite at Peter Mitchell Pit - ferroactinolite (fibrous) and grunerite (non-fibrous)
- Details of bioassays and effects provided in Coffin et al. *Toxicology Letters*, 1982
- Details of quantitative dose-response analysis provided in Cook et al. *Toxicology Letters*, 1982



F/A ReP: 7.8 104 11.6

G/A ReP: <0.7 <200 <2.7



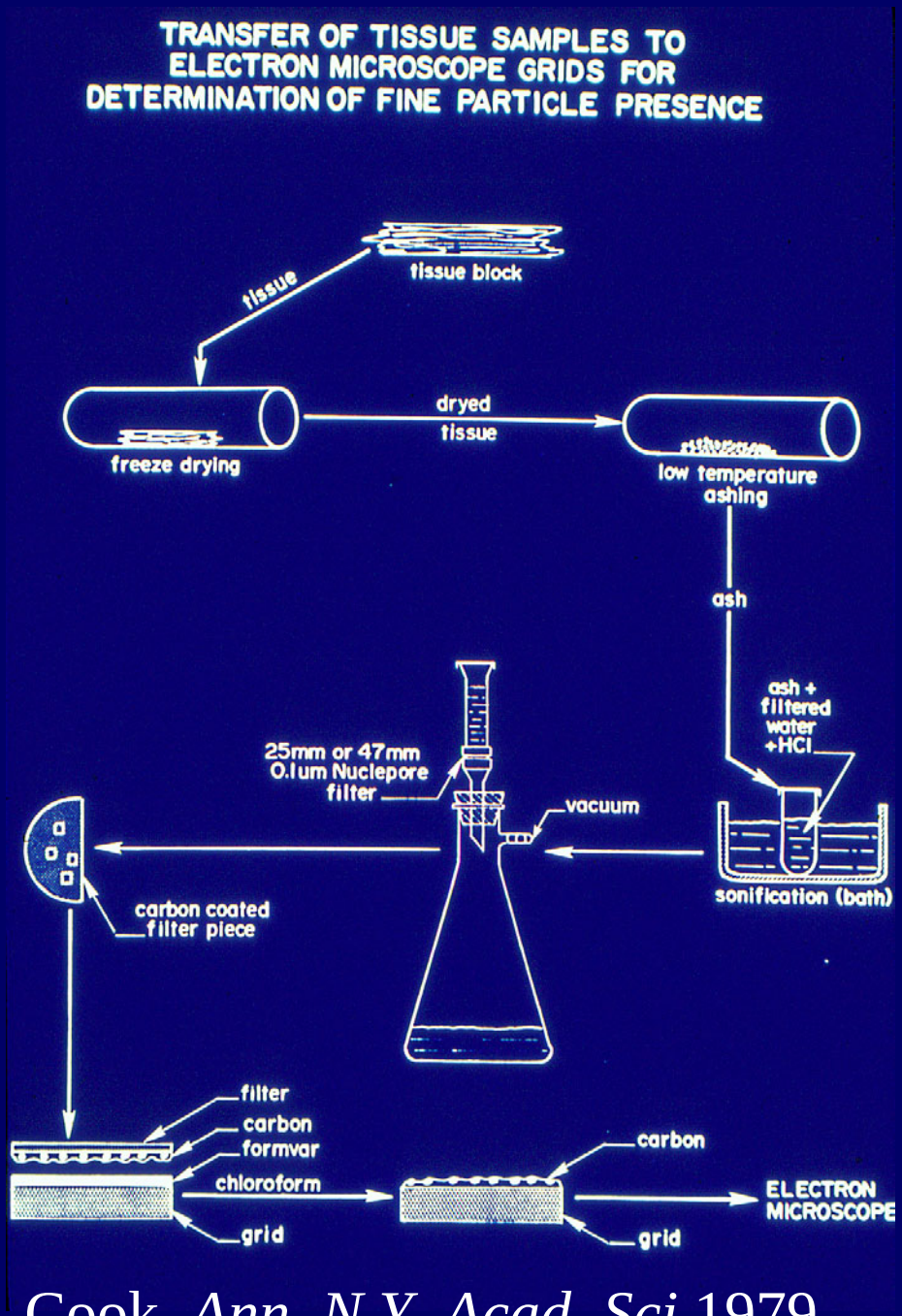


F/A ReP:	**4.7**	**62**	**11.6**
G/A ReP:	**<0.3**	**<70**	**<1.6**

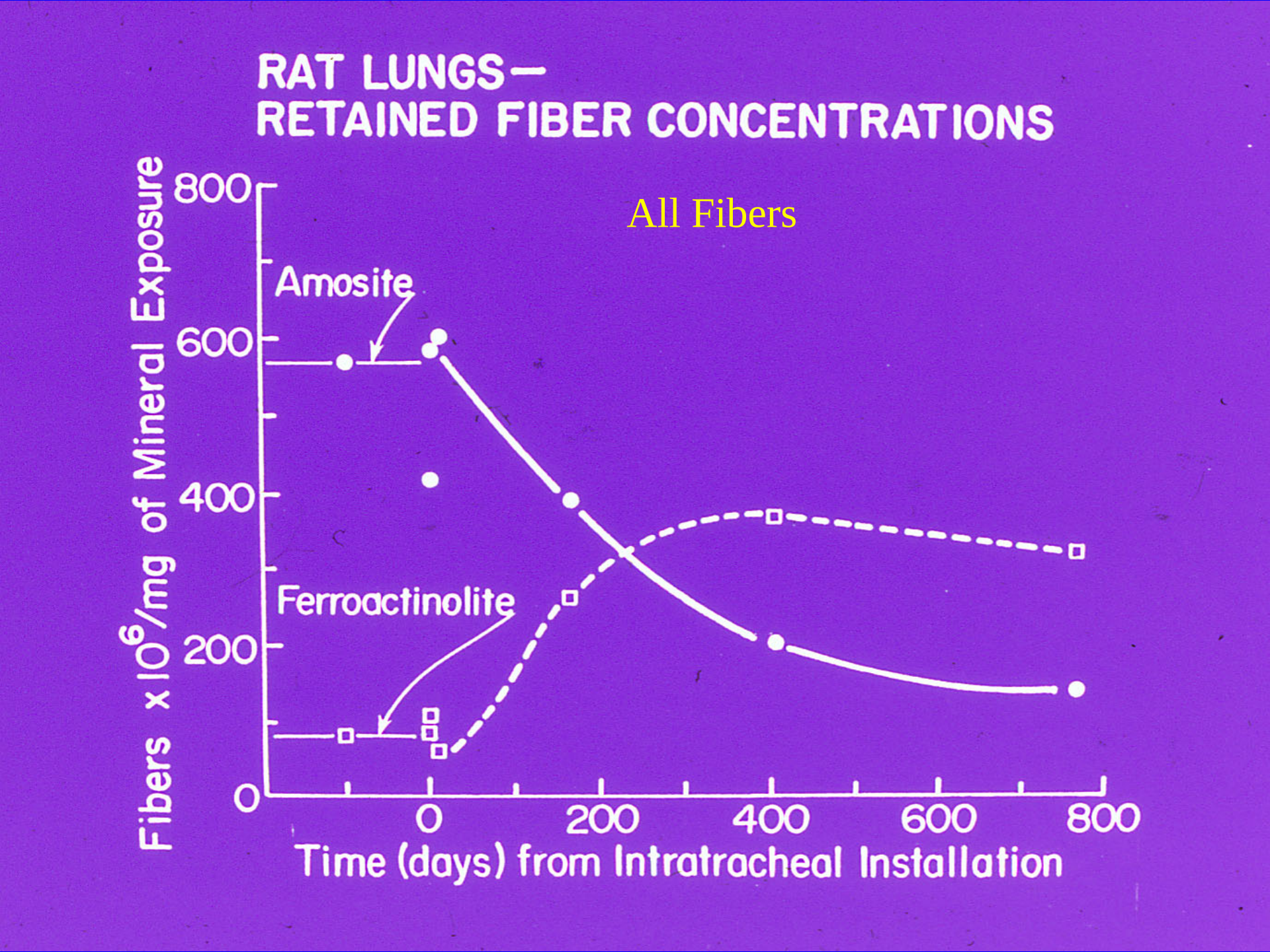
Why did ferroactinolite appear to be so potent?

Quantitative TEM analyses of whole lung samples from rats over the two year test period provided complete dose characterizations over time.

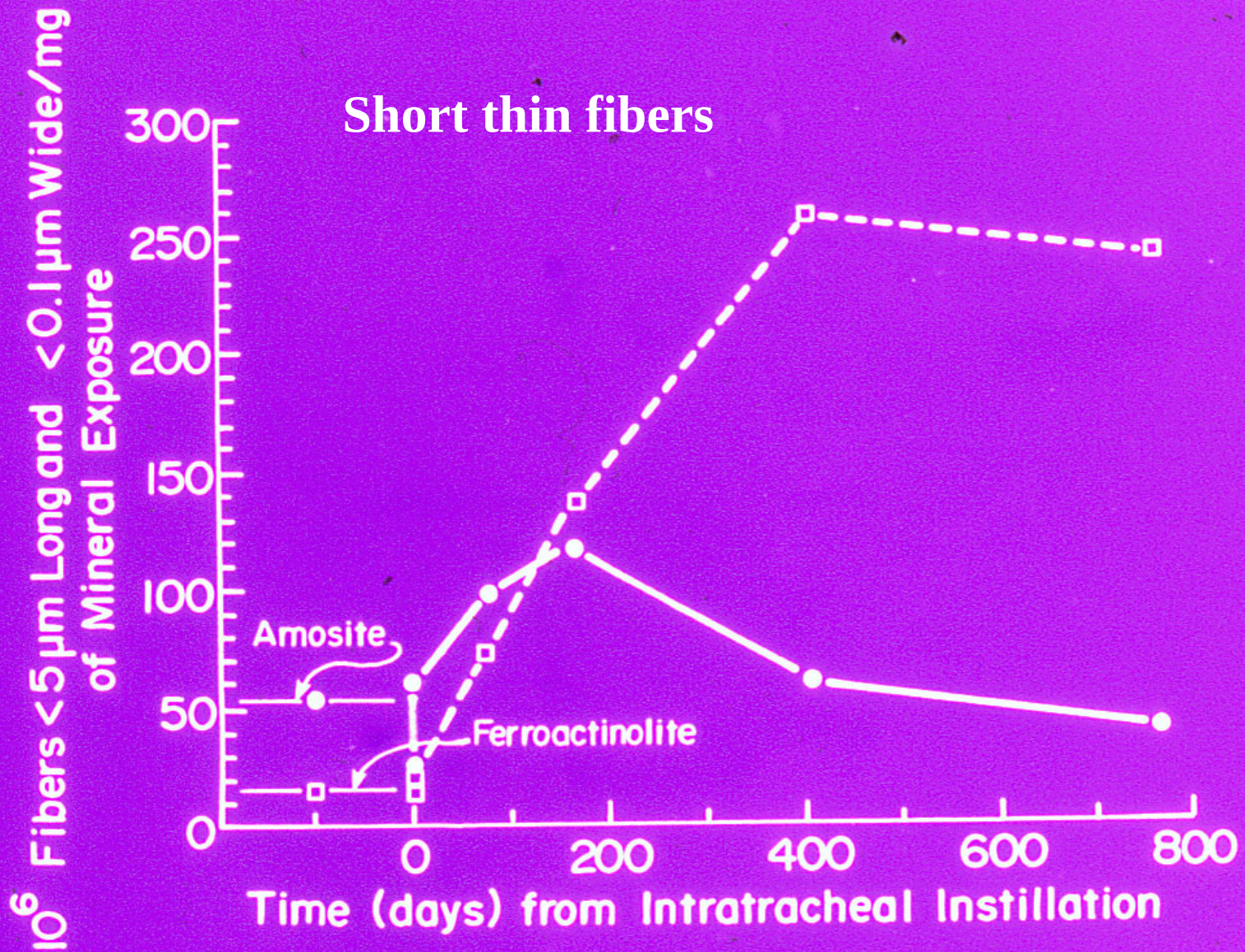
Cook et al. *Toxicology Letters, 1982*



Cook, *Ann. N.Y. Acad. Sci* 1979

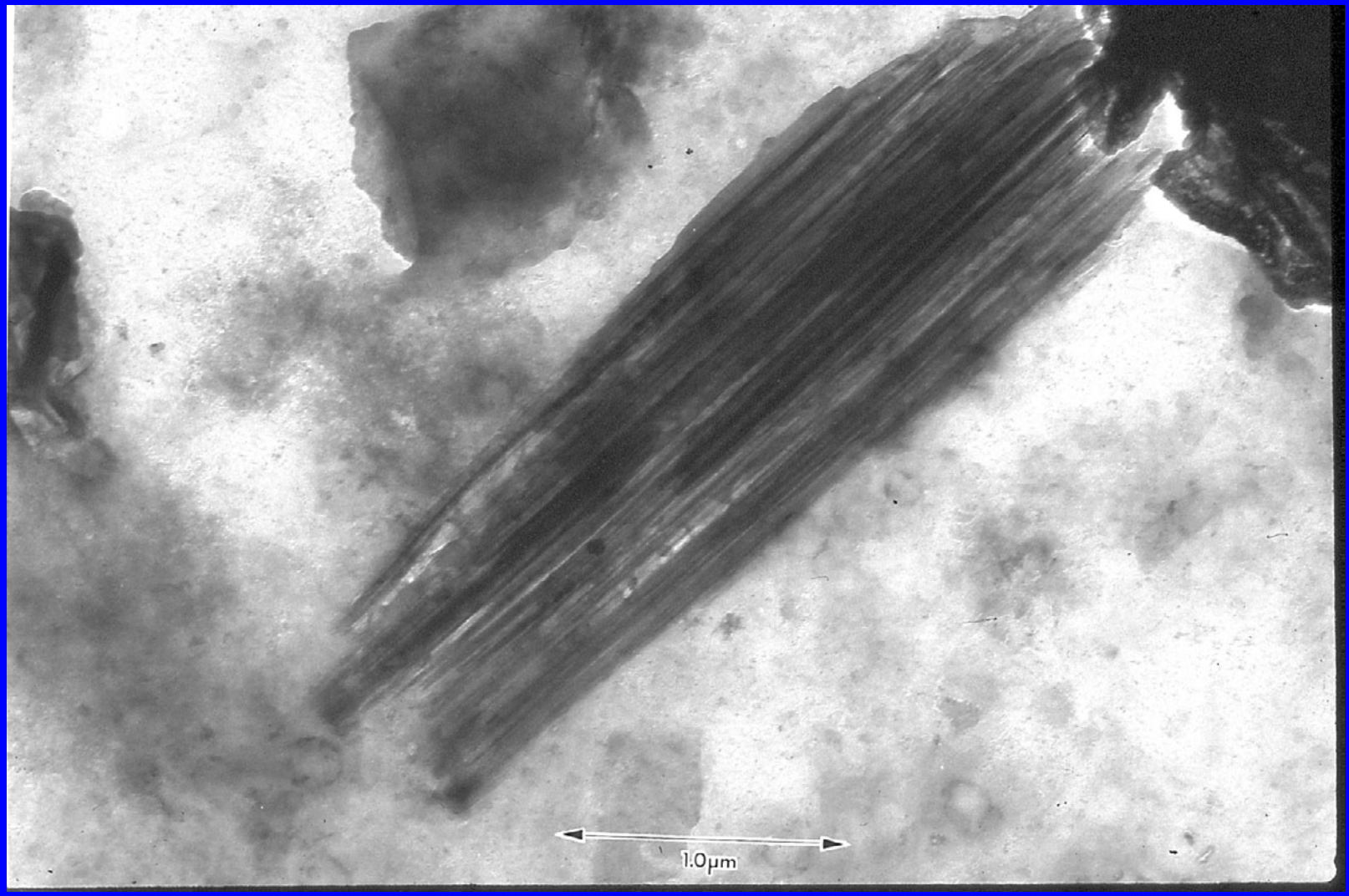

RAT LUNGS–
RETAINED FIBER CONCENTRATIONS
All Fibers
Amosite
Ferroactinolite
Fibers x 10⁶/mg of Mineral Exposure
800
600
400
200
0
0
200
400
600
800
Time (days) from Intratracheal Installation

Short thin fibers

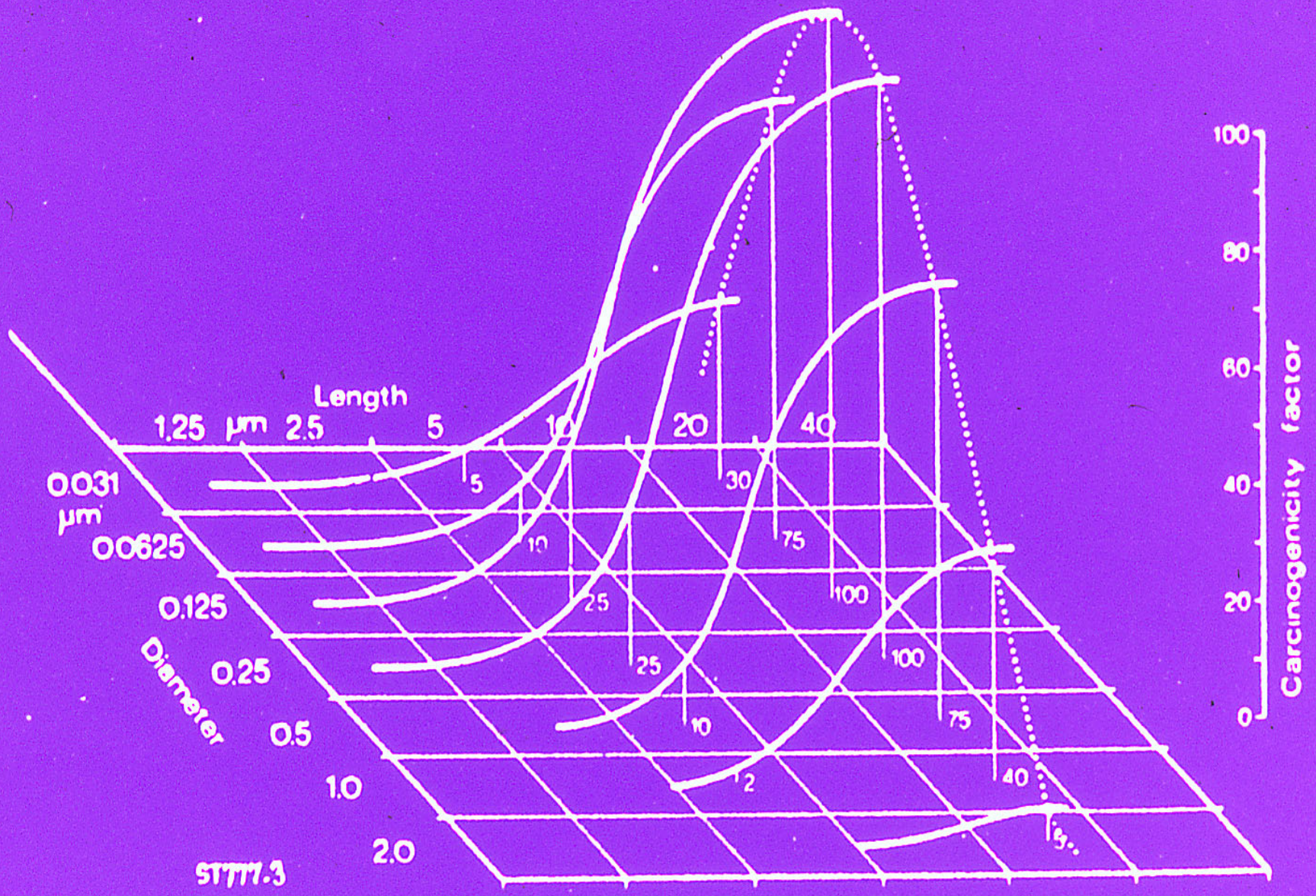


Eureka!

ferroactinolite fibers were dissolving and splitting longitudinally while residing in rat lung tissues over time.

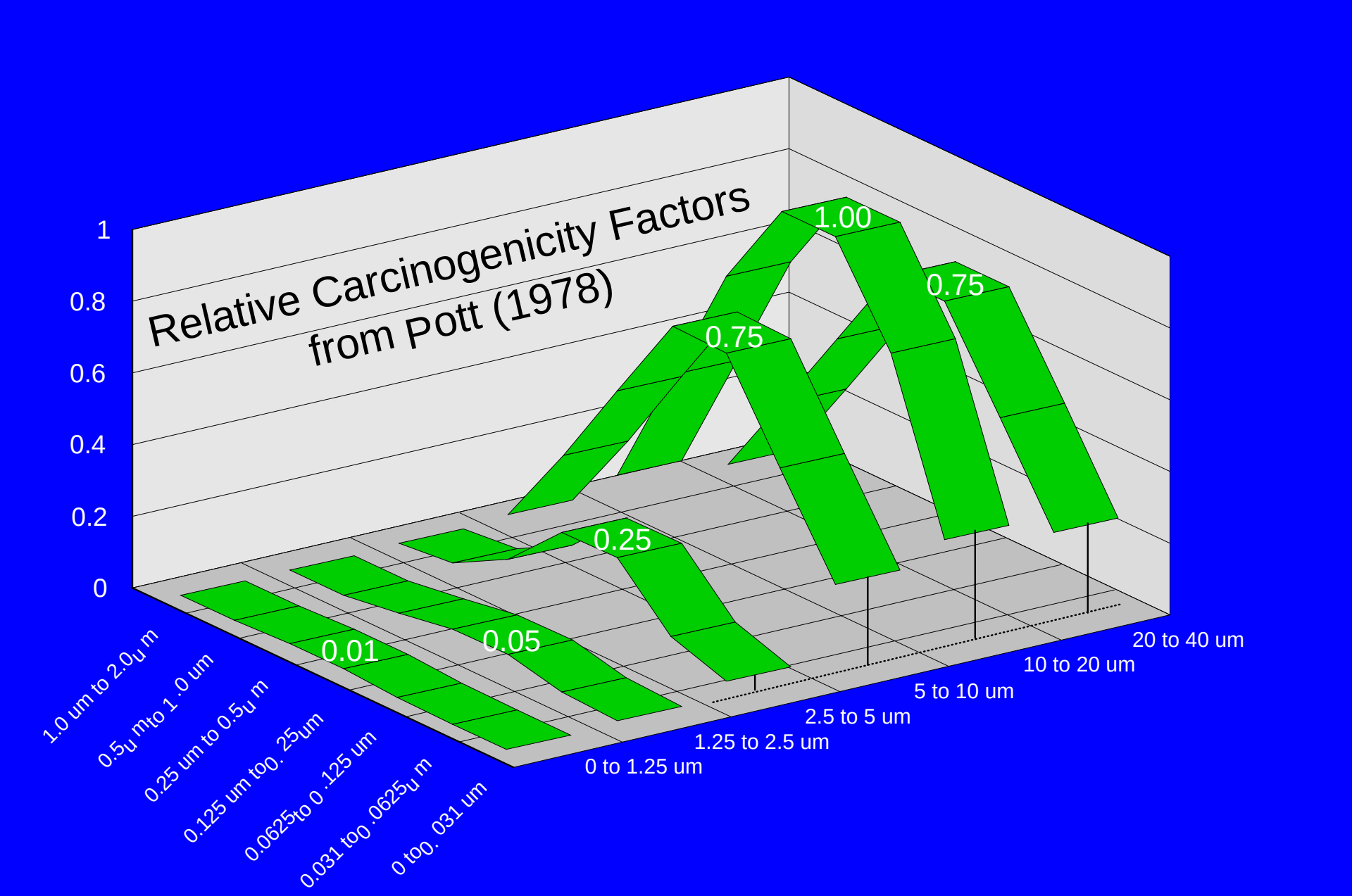


Anthophyllite in human lung



Conceptual Model for Carcinogenic Potency - Pott, 1978

(This three-dimensional model requires the fibre sizes of a sample to be divided into numerous categories. The size categories include three parameters: length, diameter and the length/diameter ratio)

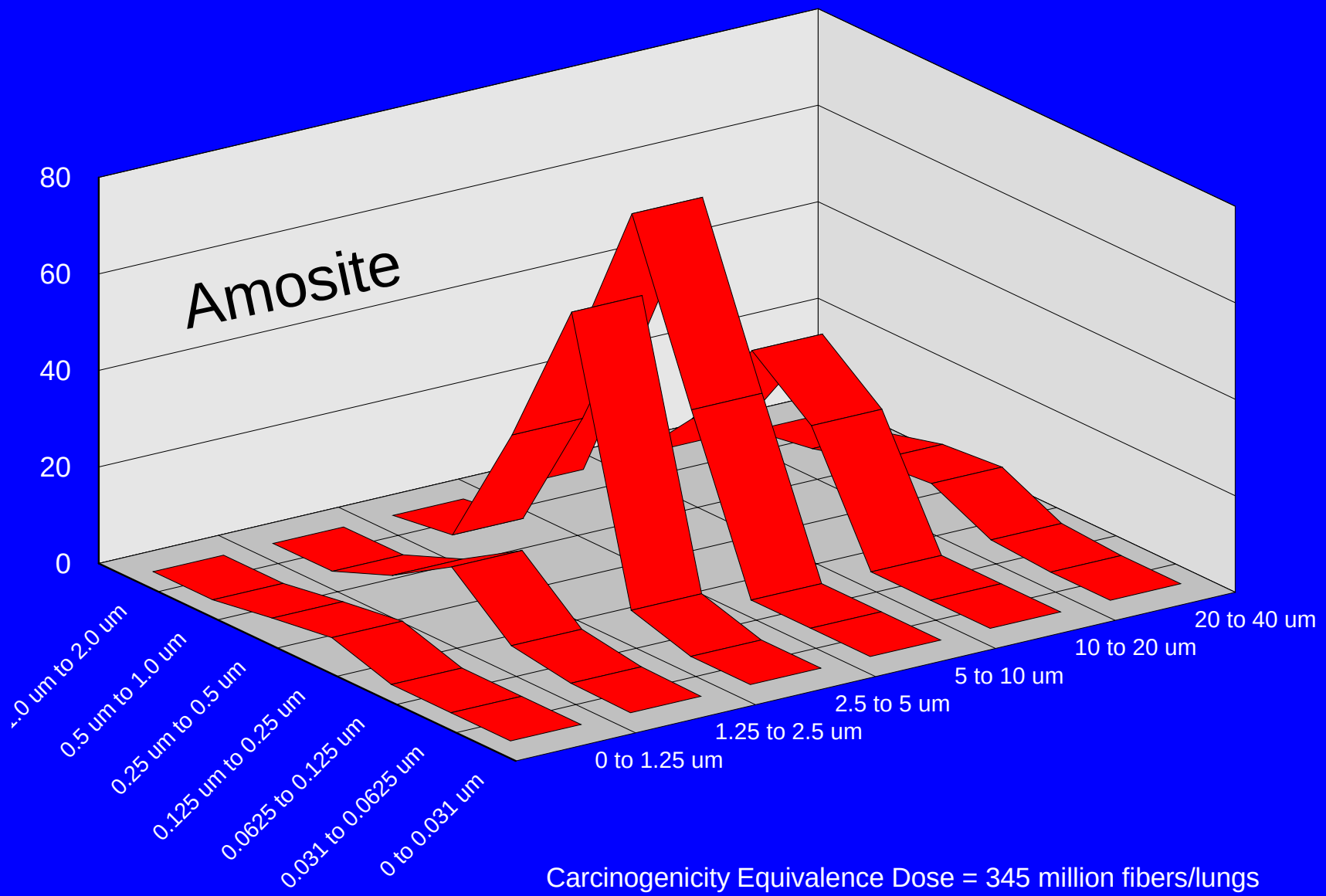


RCF = fraction of maximum potency/fiber

Carcinogenicity Equivalence Dose (CED)

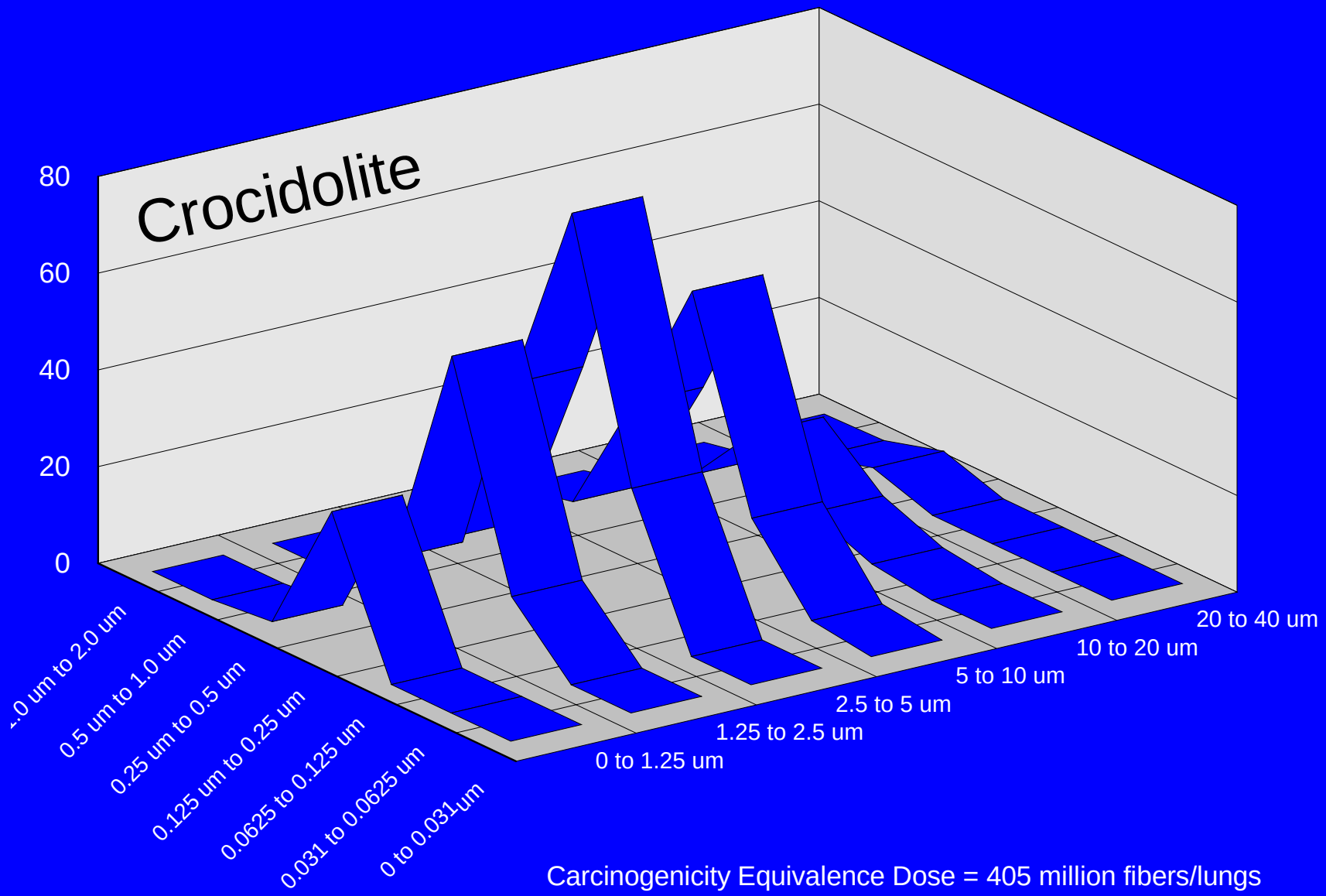
- A CED is the number of most potent fiber equivalents in the lung or pleura that results in a defined % of tumors.
- CED = $\Sigma(RCF_{i,j})\,(C_{i,j})$, where $C_{i,j}$ = # fibers/organ, RCF is the relative carcinogenicity factor (0 - 1), and i,j defines each of i△j length/width categories.
- The smaller the sample's CED, the greater the predicted potency for individual fibers.
- If amphiboles have equipotent fibers within specified size and shape ranges and the associated RCF values are reasonable, CEDs should be similar.

Rat Intratracheal Instillation



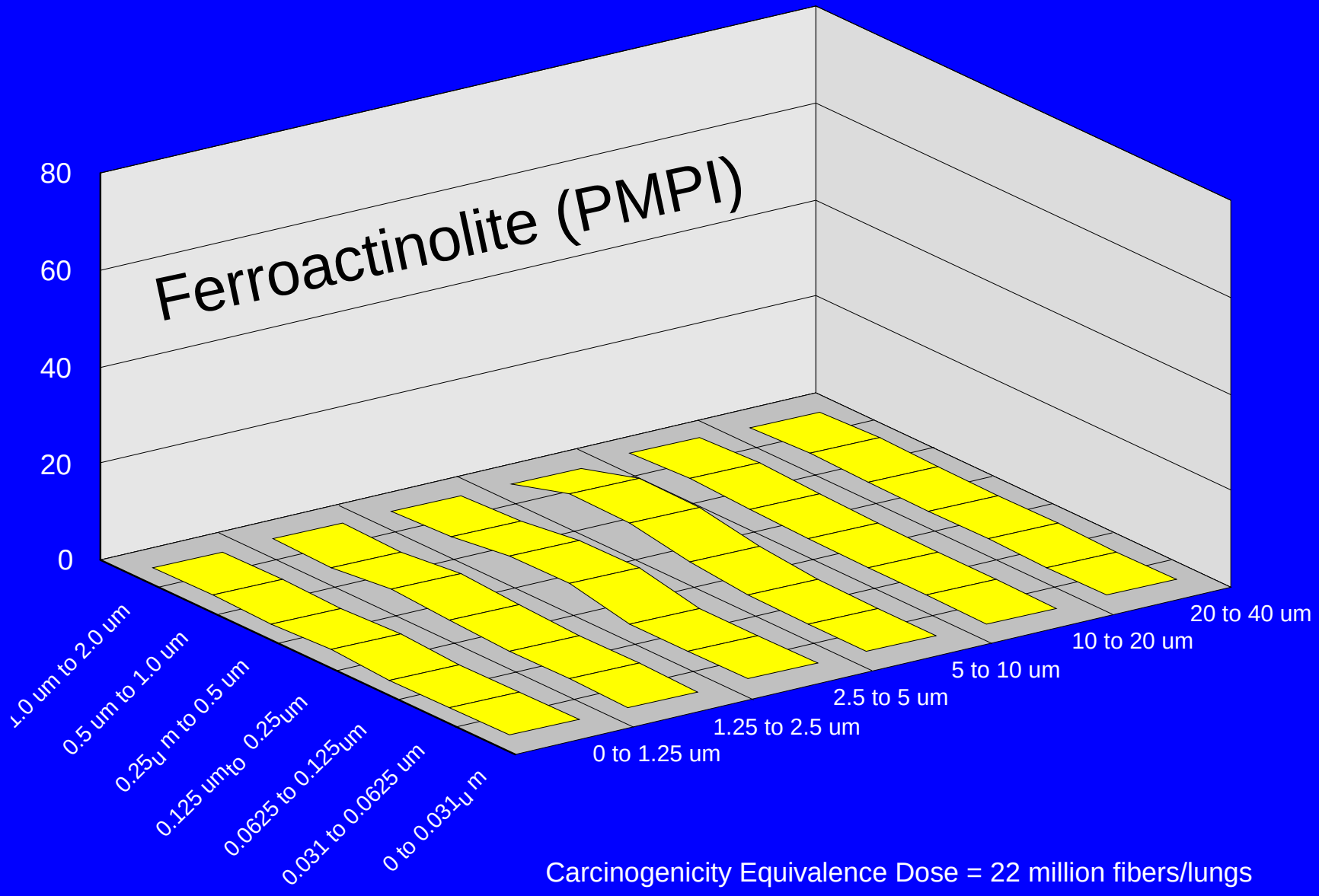
Carcinogenicity Equivalence Dose = 345 million fibers/lungs

Rat Intratracheal Instillation



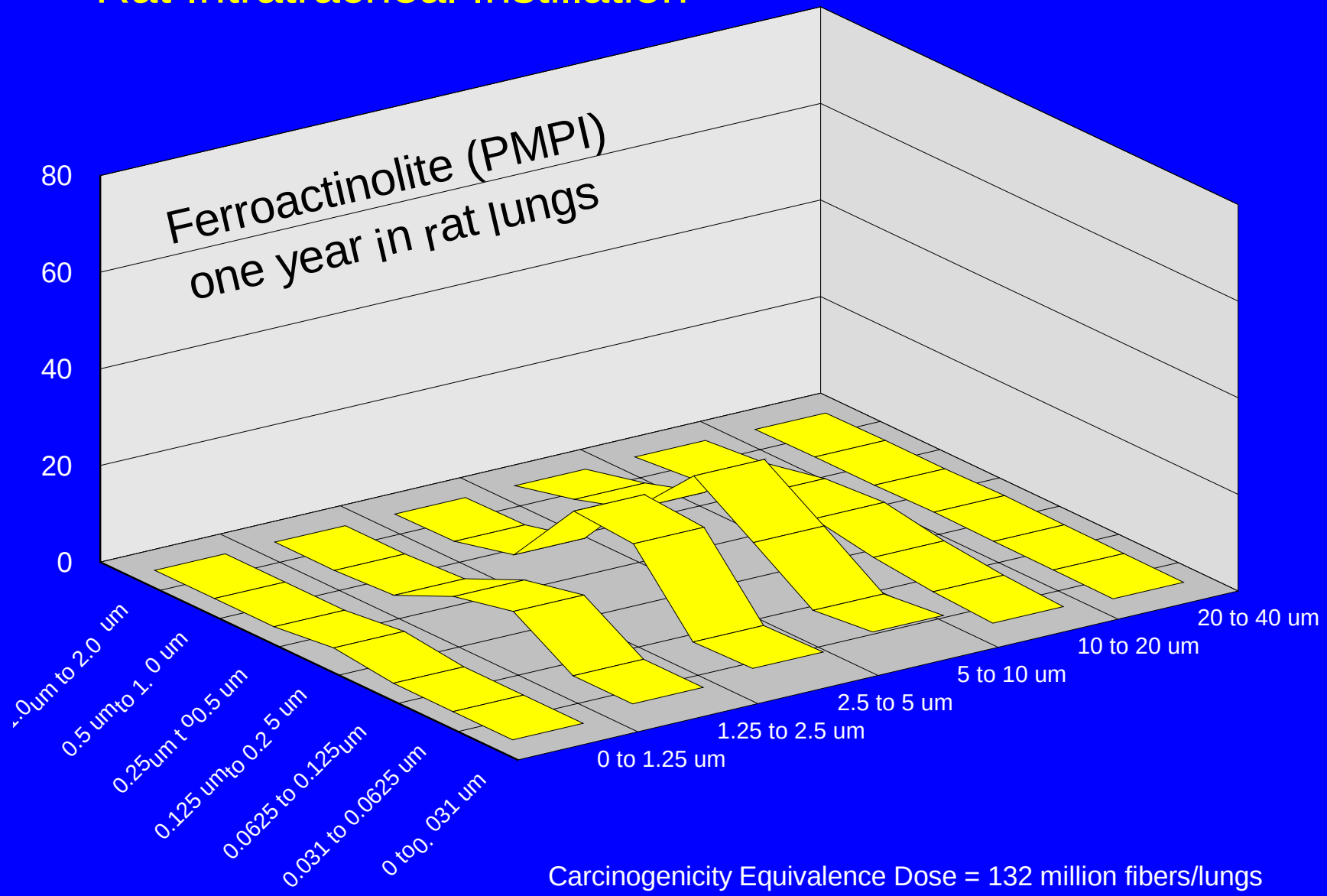
Carcinogenicity Equivalence Dose = 405 million fibers/lungs

Rat Intratracheal Instillation



Carcinogenicity Equivalence Dose = 22 million fibers/lungs

Rat Intratracheal Instillation



Carcinogenicity Equivalence Dose = 132 million fibers/lungs

Summary of fiber carcinogenicity equivalence doses (CEDs) from relative carcinogenicity factors (RCFs) based on Pott's hypothesis

Units for CEDs are millions of most potent fibers in lung per 5% tumors (IT) or in pleura per 30 % tumors (IP)

	amosite	crocidolite	ferroactinolite	ferroactinolite – one year	non-fibrous grunerite
Intratracheal	**345**	**404**	**22**	**132**	**> ?**
Intrapleural	**1149**	**539**	**72**	**441**	**> ?**

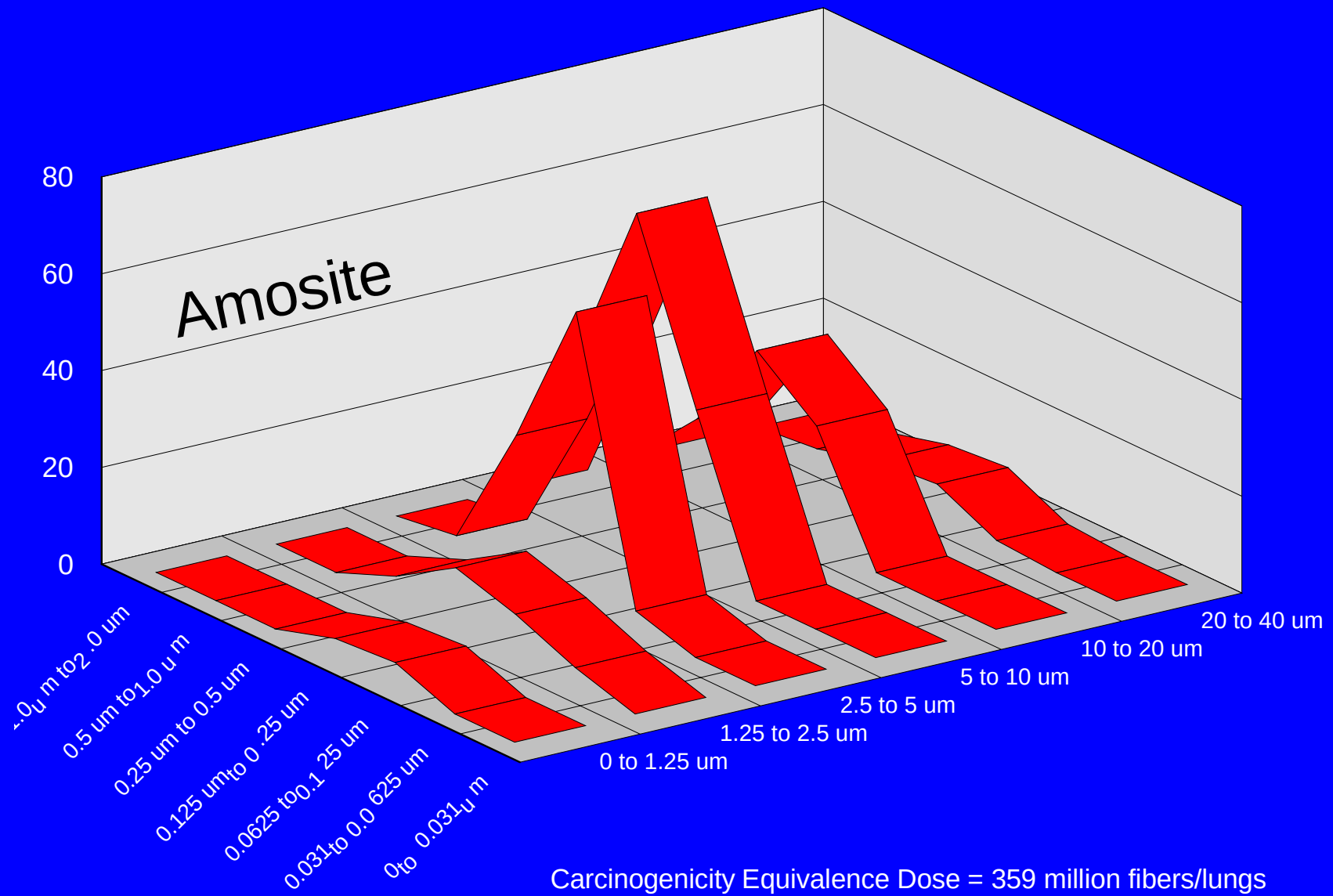
The greater the CED, the less potent the amphibole (if RCFs are accurate)

Proposal: greater RCFs for short and thin fibers than those proposed by Pott should be investigated and considered.

Adjust Relative Carcinogenicty Factors to Determine Optimum Values

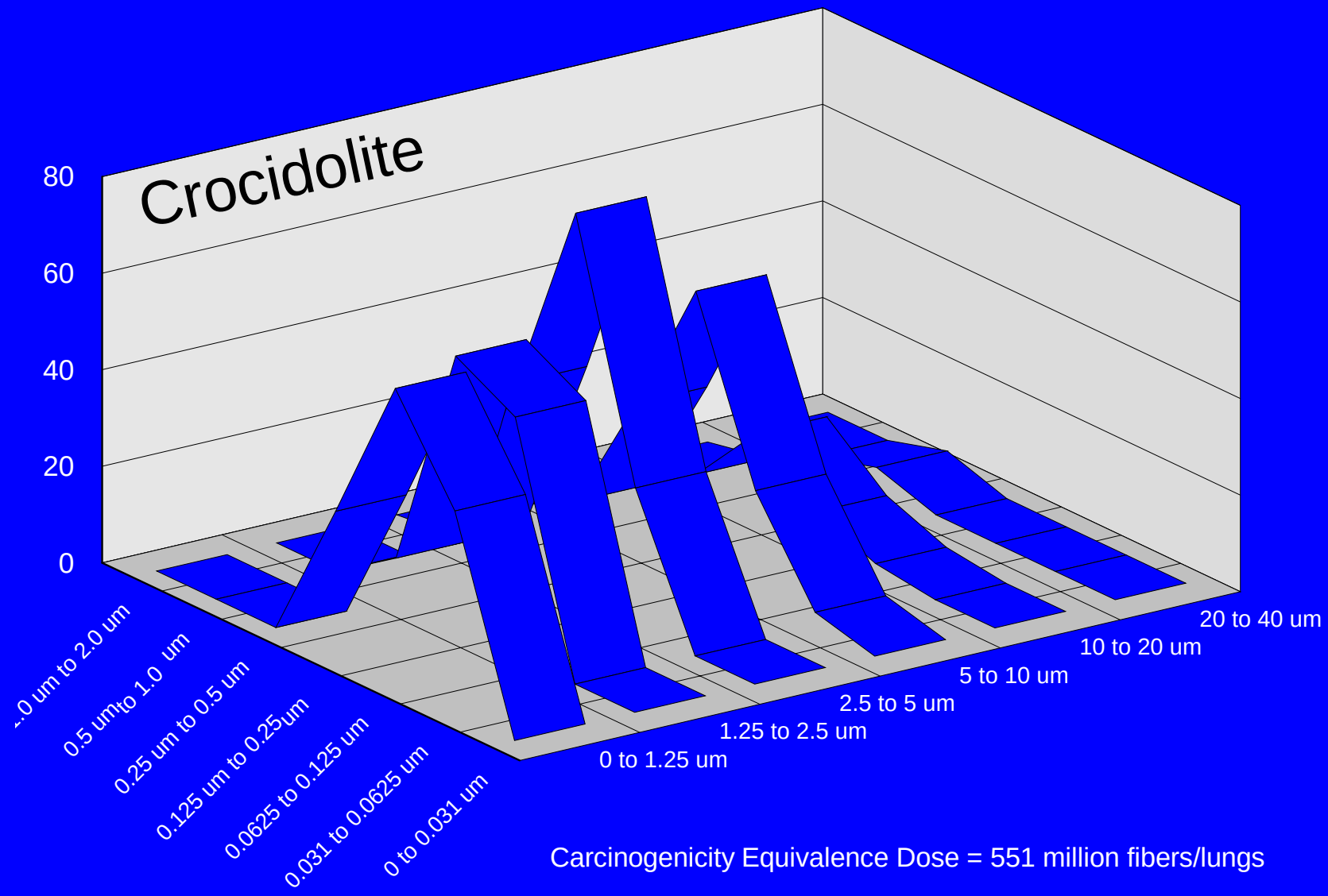
- Pott assumed short fibers have very low potencies and did not increase potency of very thin fibers.
- Cook suggests modest increase of RCFs for short, thin fibers.
- If all amphibole fibers have potencies primarily determined by fiber size and shape, carcinogenicity equivalence doses should be similar.

Rat Intratracheal Instillation



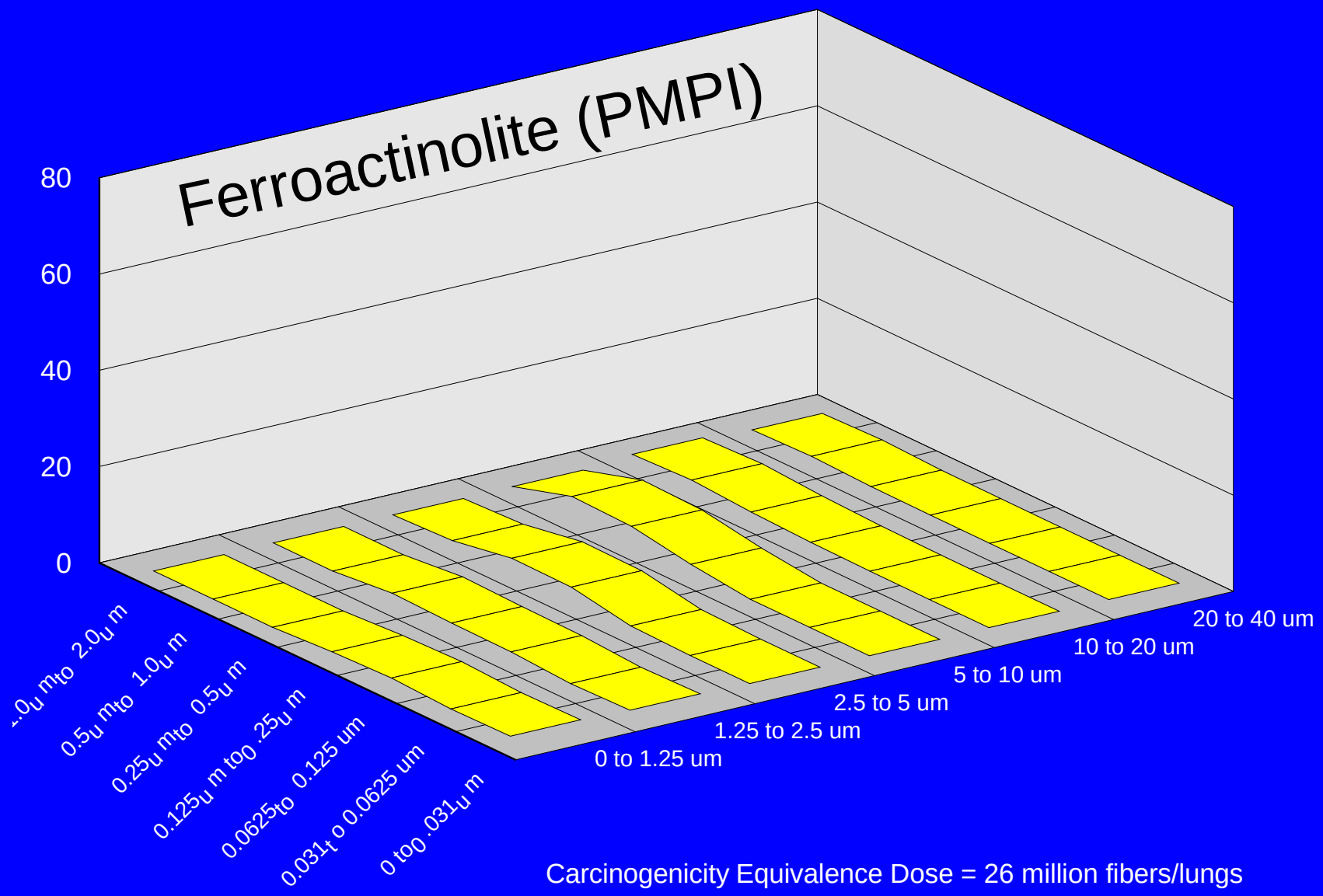
Carcinogenicity Equivalence Dose = 359 million fibers/lungs

Rat Intratracheal Instillation



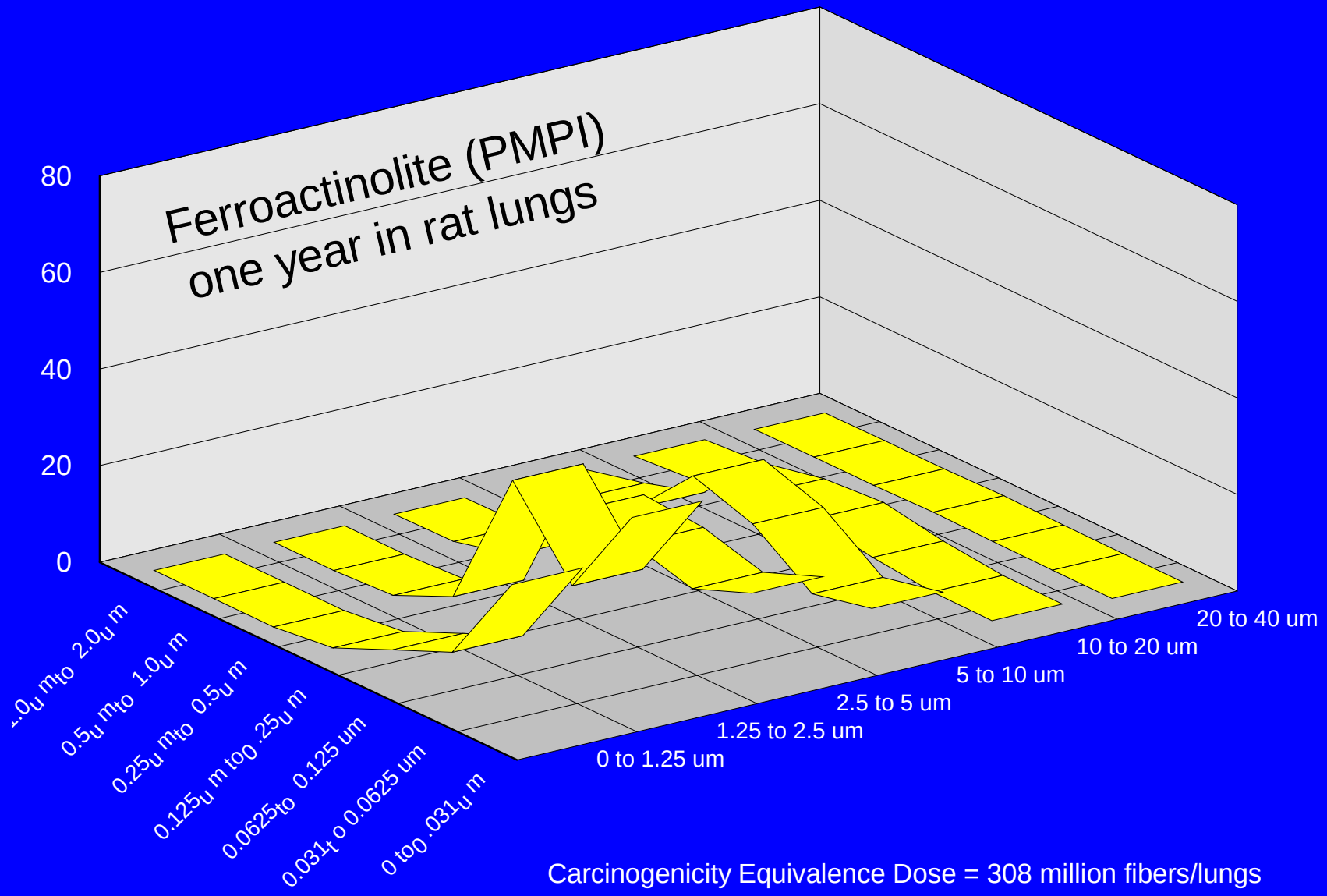
Carcinogenicity Equivalence Dose = 551 million fibers/lungs

Rat Intratracheal Instillation



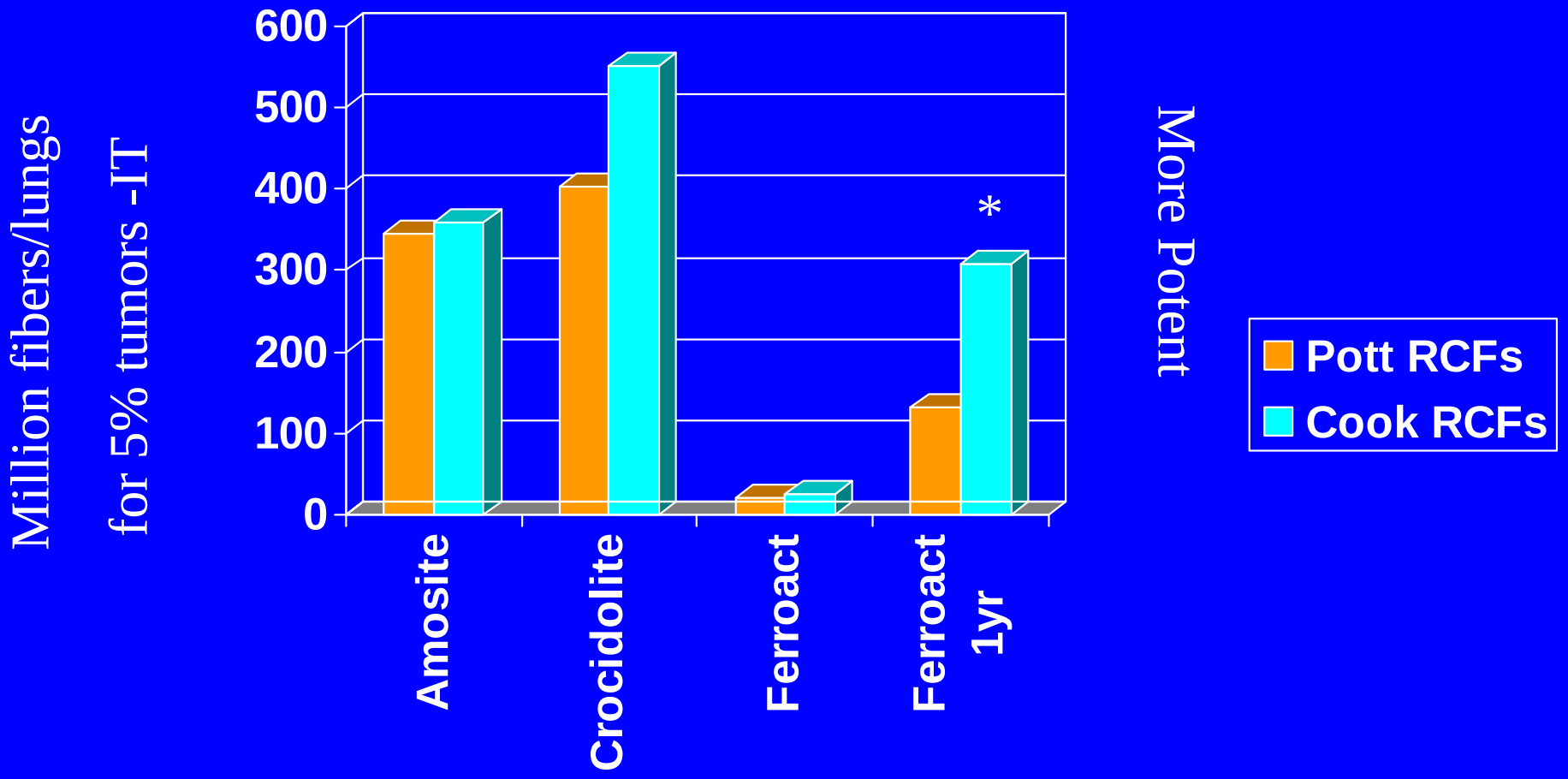
Carcinogenicity Equivalence Dose = 26 million fibers/lungs

Rat Intratracheal Instillation



Carcinogenicity Equivalence Dose = 308 million fibers/lungs

Carcinogenicity Equivalence Doses with Alternative RCFs



* For Cook RCFs, Amosite and Crocidolite CEDs at 1 year & Ferroactinolite CED at 1 year.

Conclusions

- **Fiber splitting *in vivo* greatly enhanced the potency of ferroactinolite in rat studies.**
- **Short and thin amphibole fibers appear to affect toxicity. If not, long ferroactinolite fibers would have to be regarded as many times more potent than long amosite or crocidolite fibers.**
- **Fiber numbers and sizes retained in the lung are more related to risks than the numbers and sizes of fibers inhaled. Fiber durability relates to this consideration. Fiber retention time relationships for human disease risks are uncertain.**

Conclusions continued

- **Because risk is a function of cumulative fiber dose, exposures should be measured on the basis of all fiber sizes with consideration of relative carcinogenicity and fibrogenicity of different size and shape categories.**
- **Similarly, exposure predictions should be based on all fiber sizes so that relative potencies can be included in risk assessments.**
- **Quantitative TEM analyses may be used to calibrate PLM, XRD, and other analytical methods which can not directly measure all fibers.**